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## RECENT TRENDS IN HYSTERECTOMY IN GYNÆCOLOGICAL AND OBSTETRIC PRACTICE

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THE MEDICAL and lay press are endowed rather frequently with critical reviews of hysterectomy operations. The apparent lack of agreement regarding the indications, surgical approach, and type of operation makes this an intriguing and provocative subject, and of wide and varied interest. Although of primary concern to the gynecologist, the problem of hysterectomy is also of great importance to the general surgeon and the general practitioner. However, responsibility for continued study and investigation in the field resides with the gynecologist, for it is he who is usually called upon to justify and defend the medical profession's attitudes.

It is not the intention of this paper to review the entire subject, but to discuss recent trends as they exist at The New York Lying-In Hospital. Accordingly, the investigation covers the seven-year period from 1950 to 1956, during which time 3233 hysterectomies were performed by the resident and attending staffs. This figure accounted for 23.4% of all patients subjected to surgery on the gynecological service. The average number of hysterectomies per year was 462. Of the operations performed, 74.9% or 2421 were total abdominal in type; 3.7% or 120 were subtotal; 18.2% or 587 were vaginal and 3.2% or 105 were radical procedures with lymph node dissection. These figures are probably representative in at least some respects of

many clinics throughout the United States and Canada.

It was not until after the war, during the years 1946 to 1948, that the abrupt shift on our service from subtotal to total hysterectomy occurred. Total hysterectomy was attempted on a large scale and proved so successful that the more conservative approach was generally found to be unnecessary. The initial success of this program depended upon the availability of penicillin, sulfonamides, and blood. Antibiotics and transfusion greatly diminished the danger of peritonitis and hæmorrhage, and resulted in operative risks similar to those in subtotal hysterectomy cases. Fig. 1, which covers the years

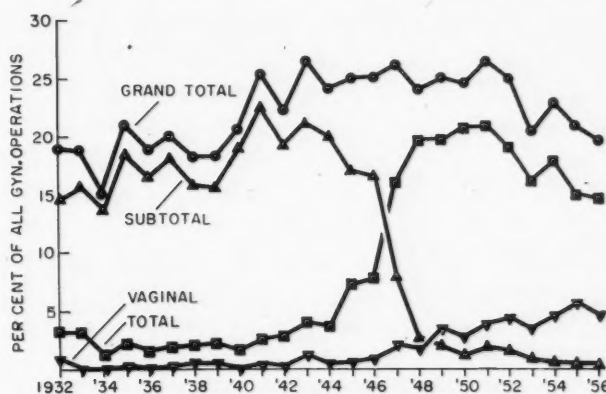


Fig. 1.—Hysterectomies in the gynecological service of the New York Lying-In Hospital, 1932-1956.

from 1932 to 1956, demonstrates a consistent pattern of subtotal procedures until 1946, followed by a rapid reversal in the two succeeding years to total abdominal hysterectomy. This shift has continued until now and currently the ratio is 1:57. Only six subtotal hysterectomies were performed in the year 1956. Supracervical operations are generally reserved for patients with severe pelvic inflammatory disease, endometriosis, or extensive ovarian carcinoma. In these instances, total hysterectomy may be considered hazardous or unnecessary, and would only prolong the operative time,

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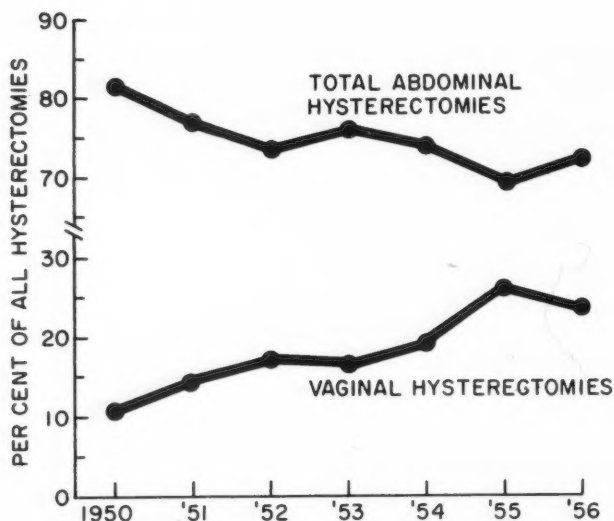


Fig. 2.—Hysterectomies in the gynaecological service of The New York Lying-In Hospital, 1950-56.

endanger associated pelvic viscera, or increase the morbidity rate.

Whereas vaginal hysterectomy was commonly employed in some institutions for a long time, it was used infrequently by us before 1949. Currently, it is performed, along with colporrhaphies, for descensus uteri or for benign disease of the uterus. In 1950 it accounted for only 11% of all hysterectomies, but by 1956, its incidence had more than doubled to 23.3%. Fig. 2 illustrates this gradual rise, with a peak incidence in 1955 of 26.3% followed by a slight drop in 1956. From present indications we would expect this figure to remain at around 25% of all hysterectomies, or somewhat over 100 cases per year. The incidence of vaginal hysterectomy in some areas is as high as 35 to 45% and in a number of institutions even higher.

We have utilized the surgical approach in selected patients as a part of the treatment for carcinoma of the cervix. Six pelvic eviscerectomies and 99 radical hysterectomies with lymph node dissection or 3.2% of all hysterectomies were performed for invasive carcinoma of the cervix and/or the corpus uteri. These usually followed preoperative irradiation. However, these data are included for the sake of completeness and will not be discussed further.

#### AGE DISTRIBUTION

Hysterectomy has been performed in almost all age groups, although the peak incidence is in the fifth and sixth decades of life. The median

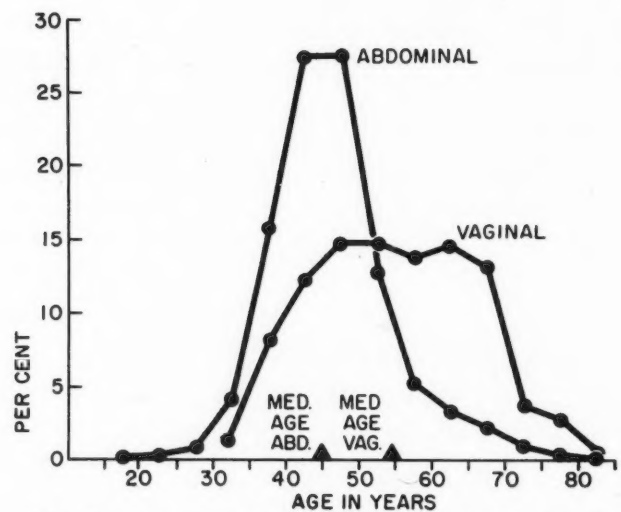


Fig. 3.—Age distribution in hysterectomies in the gynaecological service of The New York Lying-In Hospital, 1950-1956.

age (Fig. 3) for abdominal hysterectomies, which are carried out most frequently for uterine and adnexal disease, is 45.3 years, whereas the median age for vaginal hysterectomies is 54.6 years. Such a distribution is to be expected in view of the frequency with which vaginal hysterectomy is done for relaxation of the vaginal outlet and descensus uteri. The same figure also indicates that the peak percentage of vaginal hysterectomies occurs in the 20-year span between ages 45 and 65, whereas abdominal hysterectomy has a peak of only 10 years between the ages of 40 and 50.

The number of hysterectomies done in the younger age groups is of extreme importance and often is not too well emphasized. Those patients under 35 years of age account for 5.1% of the abdominal procedures and 1.2% of the vaginal hysterectomies. When this operation is carried out on a young nulliparous woman for benign disease it is a great tragedy, whereas in a parous patient who is satisfied with her family this is not necessarily the case. Carcinoma of the uterus, cervix, or ovaries was the indication for laparotomy in 27% of these patients. An additional 28% had endometriosis. Pelvic inflammatory disease also may be a most valid indication in this age group, and occasionally, prolapse of the uterus in a parous woman. For this latter condition we prefer the Manchester operation. However, hysterectomy for myomata, endometriosis, or carcinoma in situ should usually be avoided. Grave psychological trauma may follow such a procedure on a young woman. Our surgical approach may be flawless, yet we may do irreparable damage to a woman's



emotional temperament by this operation at age 30 or 35.

#### ANÆSTHESIA

General anæsthesia has been the choice in nearly all cases. Thiopentone (Pentothal) induction followed by nitrous oxide-oxygen-ether or cyclopropane is employed commonly. Spinal and local techniques are rarely used.

#### INDICATIONS

It was not feasible to review all records for the primary operative indication for hysterectomy. Instead we arbitrarily chose the year 1954. The preoperative diagnosis and the approach to hysterectomy are listed in Table I.

TABLE I.—THE NEW YORK LYING-IN HOSPITAL  
HYSTERECTOMY (GYN.) 1954  
PREOPERATIVE DIAGNOSIS AND ROUTE OF OPERATION

Diagnosis	Number	Abdominal per cent	Vaginal per cent
Myomata.....	212	96	4
Pelvic inflammatory disease.....	14	100	0
Endometriosis.....	17	100	0
Adenomyosis.....	9	78	22
Mass—cyst.....	38	97	3
Bleeding—nonspecific	22	73	27
Bleeding—functional	5	100	0
Prolapse.....	80	3	97
Malignant.....	48	96	4

As expected, myoma is the most frequent indication for the abdominal operation, whereas prolapse takes an equal position for the vaginal procedure. The indication for surgery in pelvic malignant disease and ovarian neoplasms can usually be established. The need for surgery in pelvic inflammatory disease, endometriosis and bleeding disorders is often determined only after prolonged periods of observation. Adenomyosis may be a difficult preoperative diagnosis to reach, since menorrhagia is often the only complaint. Frequently the uterus is symmetrically enlarged and softened. A diagnostic dilatation and curettage may make it possible to differentiate the condition from functional bleeding.

A pelvic examination following catheterization of the bladder under anæsthesia is performed before every operation. This procedure is of great value in establishing the diagnosis. In 80 cases of prolapse of the uterus and 48 patients with preoperative histologically recognized malignant disease, the diagnosis was of course accurate.

Myomata in patients who were often observed and repeatedly examined were diagnosed correctly in 89% of cases, pelvic inflammatory disease in 79%, and endometriosis in 47%. An ovarian cyst, which can be confused with a bowel lesion or a pedunculated myoma, was confirmed in only 74% of patients. The figure for "nonspecific bleeding" indicates that an unsuspected pathological lesion was discovered. Sixty-seven per cent accuracy for adenomyosis still leaves much to be desired.

#### TECHNIQUE OF OPERATION

The technique employed in total abdominal hysterectomy is a modification of either the Richardson<sup>1</sup> or the Aldridge<sup>2</sup> methods, except when adenocarcinoma is present, at which time varying amounts of the parametrium, in selected cases the pelvic lymph nodes and a generous vaginal cuff are removed. A Pfannenstiel or midline incision is employed, depending largely on the size of the tumour. Fine 00 chromic catgut is used. The entire abdominal contents are explored and an incidental appendectomy is performed. A variation in either the Heaney<sup>3</sup> or Bissel-Goff<sup>4</sup> technique is used for vaginal hysterectomies. In this operation the uterosacral ligaments are plicated before or after the closure of the peritoneum, and an anterior and posterior repair is routinely incorporated in the procedure if a cystocele or rectocele is present.

#### COMPLICATIONS

Almost all hysterectomies are performed to improve health, decrease physical disabilities, and/or to increase the life expectancy of the patient. Very few are done as emergency procedures. Therefore, most patients should be prepared prior to operation, and postoperative complications should be reduced to a minimum. However, complications were recorded in 49.6% of patients. Fortunately, most of the complications were minor in nature and were easily controlled. For the purpose of analysis we have grouped the most important complications into those relating to infection and those involving the hæmatological and vascular systems.

Infection (Fig. 4) leads the list. One out of five patients developed urinary tract complications which involved all or part of the system. Next, and accounting for 16.3%, were temperature elevations of undetermined etiology, which

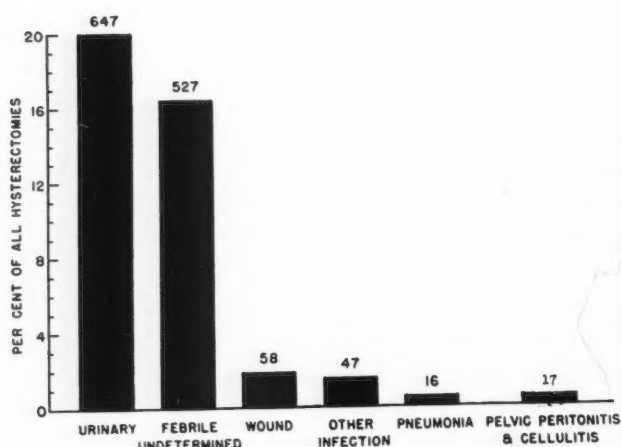


Fig. 4.—Postoperative infectious complications in hysterectomies in the gynaecological service of The New York Lying-In Hospital, 1950-1956.

could have been secondary to undetected kidney or bladder disease, local cellulitis, transfusions, or, occasionally, drug fevers. For the most part they lasted for only two to three days and responded well to antibiotics. It is anticipated that the bladder and ureters are susceptible to infection, since they are frequently imposed upon by uterine and ovarian tumours. Hydronephrosis and hydroureter as a result of pressure by pelvic tumours may encourage the development of infection. In addition, the urinary system is always traumatized to some degree during the operative procedure. The trauma is usually more extensive when repair of a cystocele is done at the time of a vaginal hysterectomy.

Of far less numerical significance are wound infections, pelvic peritonitis and cellulitis, pneumonia, and other infections. Together these cases comprise only a small percentage; all patients recovered, and few infections were of serious consequence.

Antibiotics are used liberally. They are not prescribed routinely but were employed in 74% of the patients for prophylactic or therapeutic reasons. Although there has been much discussion about the improper use of these drugs, their value as a prophylactic measure in selected patients far outweighs their unfavourable effects. This is particularly true of the broad-spectrum antibiotics. The proof of their value is evident in the fact that no patient in the entire series succumbed because of infection.

Complications in the cardiovascular system (Fig. 5) occurred less frequently than those of infectious origin, but were more serious in nature. It is in this group that deaths are anticipated. At the top of this list is anaemia, which is arbitrarily defined as a condition when the 3rd-

day postoperative haematocrit is below 35. It has been shown that most patients undergoing either abdominal or vaginal hysterectomy will lose between 500 and 800 ml. of blood, while a few may lose as much as 2000 ml. Forty-four per cent of all patients require transfusions, so this figure of 9% is much lower than if blood had not been employed. Thrombophlebitis, next in frequency and the most dangerous of all our complications, occurred in 80 patients or 2.5%, some of whom required prolonged hospitalization, bed rest, and anticoagulant therapy. Of these, 16 developed pulmonary emboli and infarction. In some cases, the embolus was the first manifestation of the disorder. Haemorrhage and haematoma occurred in 72 or 2.2%, although we are inclined to believe that this is an underestimate. Previous studies of blood volume determinations<sup>5</sup> from our service have shown that large, undetected losses of blood from the circulating volume may be found postoperatively. In some instances haematomata were accessible and evacuated, while in others, though suspected, they were not drained. It was estimated that significant postoperative extravasation into tissues occurred in about 5% of the patients. Shock is very infrequent because its development is prevented by precautionary transfusion. Though atelectasis is strictly not in this group, we prefer to mention it along with cardiac complications since both are serious and require rapid and dramatic measures. They occurred in 0.8 and 0.6% of patients respectively.

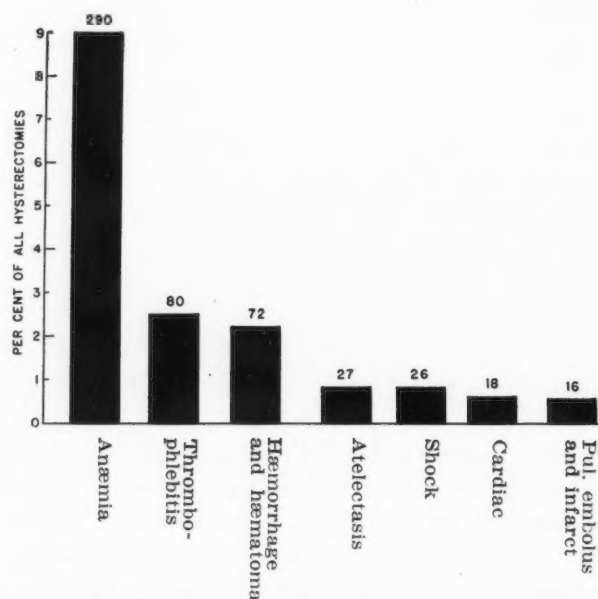


Fig. 5.—Vascular, blood and cardiac postoperative complications in hysterectomies in the gynaecological service of The New York Lying-In Hospital, 1950-1956.

It is generally believed that vaginal hysterectomy involves fewer postoperative problems. We have not found this true (Fig. 6), since almost double the number of urinary infections and ten times the incidence of urinary retention occurred in the vaginal group as compared to the abdominal group. The explanation for these figures lies largely in the frequency of cystocele repair that accompanies a vaginal hysterectomy. However, wound infections were only half as frequent and abdominal pain was seldom encountered following the vaginal operation.

#### PATHOLOGY

We surveyed the records of all patients operated on during the period from 1950 through 1956 for all lesions of the corpus uteri. We found that of the 3233 hysterectomies performed 2068 or 64% of the uteri contained myomata, and 669 or 20.7% had the submucous variety. Five hundred and thirty-six or 16.6% contained endometrial polypi, and 661 or 20.4% exhibited atrophic endometrium. One hundred and fifty-one or 4.7% had hyperplasia of the endometrium. It is not necessarily implied that the lesion justified the operation. No lesion was recorded in 120 or 3.7%, which included many uteri removed along with ovarian tumours, endometriosis or pelvic inflammatory disease.

Of special interest to us in this entire group was the number of uteri removed for carcinoma. Two hundred or 6.2% contained a malignant tumour of the cervix, and 238 had cancer or sarcoma of the corpus. While 83 of the cervical lesions were in situ, only six lesions of the corpus were recorded as such. The latter diagnoses in the corpus were made by fulfilling the pathological criteria established by Hertig. Sarcomas were found in 42 or 1.3% of the entire series, which is higher than expected. However, many of these sarcomas occurred in myomata, and in some instances differences of opinion existed with respect to the diagnosis. Most of these were unusually cellular myomata and were classified as sarcoma so that the

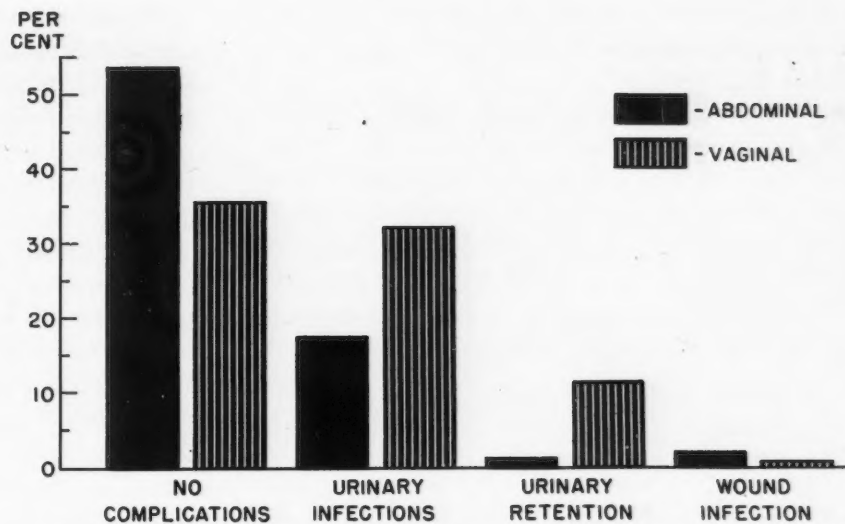


Fig. 6.—Major differences in complication between abdominal and vaginal hysterectomies in the gynaecological service of The New York Lying-In Hospital, 1950-1956.

patients would be followed up and the records would be available for further study.

Sixty-nine or 2.1% of the patients had ovarian cancers. These, of course, required primarily ovarian surgery and the hysterectomy was only an incidental part of the operation. Carcinoma of the tube was encountered in four patients, but in such cases hysterectomy is of more importance from a therapeutic point of view than in the treatment of malignant ovarian tumours. Vulvar carcinomas were included because in two instances a hysterectomy and radical lymph node dissection were performed as well as the vulvectomy.

While studying our 1952 carcinoma cases we were surprised to find that 21 out of 74 cancers were diagnosed postoperatively with no mention of their existence before operation. These 21 amounted to 4.6% of the hysterectomies for that year. Even though several lesions were in situ, this is an extraordinarily large proportion and indicates the necessity for routine cytological smears or a diagnostic dilatation and curettage for all patients who are to undergo hysterectomy. Had we known of the existence of the tumours, we might have altered our procedure, at least in some cases, to remove a larger vaginal cuff or to perform a wider parametrial dissection.

External endometriosis was found in 302 patients, or 9.3% of all hysterectomies (excluding cases in which cancer had precedence as an indication for hysterectomy). Three and six-tenths per cent had endometrial cysts of the ovary, in 4.8% the peritoneum or abdominal



viscera were involved, and in 0.9% the lesion was on the serosal surface of the uterus.

TABLE II.—THE NEW YORK LYING-IN HOSPITAL  
HYSTERECTOMY (GYN.) 1950-1956  
ENDOMETRIOSIS AND AGE—EXCLUSIVE OF CANCER

	Age			Total
	20-24	25-29	30-34	
Endometrial cyst.....	0	2	7	9
Endometriosis (Other than corpus uteri)	1	1	7	9
Endometriosis—corpus....	0	0	2	2
Total.....	1	3	16	20
Adenomyosis.....	0	3	19	22
Total including adenomyosis	1	6	35	42
Per cent age distribution...	0.1	0.6	3.2	3.9

We were interested in the number of uteri removed because of this disease in patients under the age of 35 (Table II). There were 20 with external endometriosis. Adding to these patients those who had adenomyosis, the total was increased to 42 or 3.9% of the 1081 patients with endometriosis and/or adenomyosis.

TABLE III.—THE NEW YORK LYING-IN HOSPITAL  
HYSTERECTOMY (GYN.) 1950-1956  
MORTALITY

Cause of Death	Number	
Carcinoma.....	5	
Pulmonary embolism.....	2	
Acute coronary occlusion.....	1	
Cardiac arrest.....	1	
Hæmorrhagic disease of unknown etiology.....	1	
Total.....	10	(0.3%)
Death due to operation.....	5	(0.15%)

MORTALITY

The gross mortality rate (Table III) was 0.3% and the corrected rate was 0.15%. Five patients died postoperatively before discharge from hospital as a result of carcinoma with metastases and these deaths cannot justly be attributed to the operation. Undoubtedly these five would have succumbed to carcinoma whether or not the operation was performed. However, another five died as a direct result of the operation. Two were lost because of pulmonary emboli, one following a coronary occlusion, one from cardiac arrest, and another because of hæmorrhagic disease of unknown etiology. This last patient was discharged but readmitted some weeks after operation. Transfusion, fibrinogen, and other agents to improve the clotting mechanism were administered without effect.

It is evident that the cardiovascular complications were most hazardous and that no deaths

followed infectious processes. Antibiotics have achieved an important place in our surgical care and their liberal use has averted some serious problems. As yet, even though anticoagulant drugs have reduced the death rate from coronary thrombosis and pulmonary emboli, there is still a great need for a drug that can be used therapeutically and prophylactically with the effectiveness of antibiotics.

HYSTERECTOMY ON THE OBSTETRICAL SERVICE

For completeness we felt that we should review briefly our experience with obstetrical hysterectomies. During this study period, 31,697 pregnant patients were admitted to The New York Lying-In Hospital. Of these 28,521 had deliveries and there were 3176 abortions. Eighty-three hysterectomies were performed among these obstetrical patients, giving an incidence of 0.26%. Twenty-eight operations followed Cæsarean section and 17 were performed after vaginal delivery. Eight were done at laparotomy for ectopic pregnancy, five for malignant mole or chorionepithelioma, and 10 for the purpose of therapeutic abortion; six followed other abortions, and nine were incidental with unsuspected pregnancies from our gynæcological service.

Myomata were the primary indications for these operations, although the usual reasons, namely hæmorrhage and ruptured uterus, were also represented. No mortality was associated with these 83 hysterectomies. Some were sub-total, but in recent years total hysterectomy has been done more frequently.

DISCUSSION

We have presented a panoramic picture of our recent experience with hysterectomy in The New York Lying-In Hospital. There have been two striking changes in technique. The first involves the more frequent employment of the total abdominal hysterectomy and the second the increased use of the vaginal operation. There were, as we pointed out, misdiagnoses, the most serious of which concerned the removal of an unsuspected pregnancy or an unrecognized carcinoma. By and large, though, the criteria for a therapeutic operation were considered to be fully satisfied by each surgeon before he made his incision. Therefore, we shall not go on to belabour the argument of unnecessary hysterectomies. We offer instead a plea for individualization for each patient, since we cannot reduce the patient's well-being to a rigid

list of indications. A tissue committee is a valuable asset to a hospital organization and administration, but some tissue committees often fail to recognize certain clinical indications, physiopathology involved, or even such symptomatic anatomical defects as relaxed vaginal outlet or descensus uteri. A pathological laboratory is located in our division of the centre. It is staffed by both resident and attending members of the department of obstetrics and gynaecology. All members of the staff are on the tissue committee. About one-half of the operations, which included all of the ward material, were performed by the residents. Members of the resident staff assist at all operations performed by the private attending doctors.

From a review of our material, we offer the following suggestions. Two conditions, myoma uteri and carcinoma in situ, are often treated by hysterectomy. In the treatment of myoma uteri, a hysterectomy is usually not necessary in a young woman and is most undesirable in the young nulliparous patient. Myomectomy is a perfectly acceptable, feasible and worthwhile operation. It is exceedingly rare that we are unable to remove fibroids and not retain uterine function. It is unnecessary to sacrifice a uterus for single or multiple fibroids, if the surgeon is willing to take the time and exert the effort to perform a careful myomectomy. The second problem is that of carcinoma in situ. Many gynaecologists feel that this is a premalignant lesion and accordingly have been quite radical and performed a total hysterectomy. As more evidence is being accumulated, it is apparent that in the young patient who can be observed with smears and/or biopsies, conization or amputation of the organ may be all that is required. Such a woman may go on to bear children, and in many cases the lesion is apparently completely cured. As long as we can satisfy our pathological criteria and be certain that this lesion is limited to the epithelial layer and has not invaded the stroma, hysterectomy is not the only acceptable form of treatment.

It is recommended that cytological smears, curettage or biopsy be performed as indicated in all patients prior to laparotomy. Undoubtedly we can improve our preoperative diagnoses by obtaining those studies before proceeding with major surgery.

In a report such as this including so many patients it is not practical to attempt the justifi-

cation of every operation. Likewise it is also possible that some patients currently being followed in our clinics and by members of our attending staff would benefit by surgery. Conservatism in the presence of benign disease often involves long preoperative observation and study. The existence of benign disease or tumour in tissues removed does not necessarily justify the operation. Facilities for the study of the emotional and psychological processes may be of equal importance. The postoperative experiences should be followed for months and years. The studies must include extensive psychological observations in addition to somatic evaluation. In the final analysis the welfare of the patient depends on the moral integrity and the educational experience of the doctor, a thorough evaluation of the organic problems concerned and a penetration of psychological barriers.

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#### RÉSUMÉ

Les tendances actuelles dans la pratique de l'hystérectomie comme elles se manifestent au Lying-In Hospital de New York sont vers une plus grande proportion d'hystérectomies abdominales totales et un recours plus fréquent à l'opération par voie vaginale. L'auteur recommande fortement l'individualisation des indications opératoires, un cadre rigide ne pouvant s'appliquer à toutes les patientes. Un comité des tissus apporte sans doute une aide précieuse à l'organisation et à l'administration d'un hôpital, mais encore faut-il que ce comité reconnaisse certaines indications cliniques et soit au courant de la physiopathologie de certains cas, même de certaines anomalies anatomiques symptomatiques telles que l'élargissement de l'orifice vulvaire ou le prolapsus de l'utérus. Dans les cas de fibromyomes utérins, il est rarement nécessaire de pratiquer l'hystérectomie chez une jeune femme et on doit l'éviter à tout prix chez une nullipare. La myomectomie forme une solution satisfaisante et parfaitement acceptable. Ce n'est que très rarement que nous ne pouvons pas enlever de fibromes sans conserver la fonction utérine. Tout dépend du temps et des efforts qu'est prêt à consacrer le chirurgien pour accomplir une myomectomie soignée. En ce qui concerne le carcinome *in situ*, plusieurs gynécologues le considèrent comme une lésion pré-maligne et le traitent d'une manière radicale en pratiquant l'hystérectomie totale. Chez les jeunes femmes que l'on peut suivre de près par des frottis cytologiques ou des biopsies, l'amputation en cône peut bien être suffisante. Il suffit d'être sûr que la lésion est confinée à l'épithélium et n'a pas cherché à envahir les plans moins superficiels. La cytologie exfoliative, le curettage et la biopsie devraient toujours précéder la laparotomie car ils contribuent à préciser le diagnostic pré-opératoire. En fin de compte le bien-être de la malade dépend non seulement de l'intégrité morale du médecin, de sa formation et de son expérience, mais aussi d'une évaluation complète des problèmes organiques de la femme et de l'abaissement de ses barrières psychologiques.



## INDICATIONS FOR GYNÆCOLOGICAL SURGERY\*

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THIS DISCUSSION of the indications for gynecological surgery represents one individual's opinions on perhaps the most important aspect of gynecological surgery, rather than a presentation of different views on very controversial questions. If some of the opinions herein expressed seem dogmatic, they will at least provoke thought and possibly healthy discussion.

In general, it should be stated that there is no indication for gynecological surgery in the case of minimal benign anatomical abnormality or derangement, when the patient has no signs or symptoms which are disturbing to her. This applies also to the patient with slight disturbances which might be corrected by conservative means.

In certain instances, the indications for a gynecological operation may not be followed by the appropriate surgical procedure because the surgeon is influenced by his training and experience rather than his judgment.

It may be that the title of this paper should have been "Contraindications to Gynecological Surgery", for in discussion of some of the topics involved, contraindications play a large role. Perhaps they are more important anyway.

### SURGERY IN INFERTILITY

The results of operations undertaken for relief of the various causes of infertility are disappointing. No rosy promises should be held out to the patient, and indeed unless she demands that something more be done, major operations should not be encouraged. While there are happy exceptions to this dismal outlook, Bayard Carter<sup>1</sup> and associates showed that, in comparison with a control group presenting the same abnormalities, certain operations for relief of infertility actually reduced fertility. These included cervical operations, suspensions, excision of ovarian cysts, and tubal operations. They found that these operations are usually done casually and without adequate study of the couple involved.

In the first place, no operation should be attempted until the patient has been carefully examined for disease which might contraindicate pregnancy, and the sperm, postcoital, and Rubin tubal patency tests have shown normal results. The only exception to this is the patient who has had a previous pelvic infection, or peritonitis from a ruptured appendix or other viscus, and who shows repeatedly negative Rubin's tests and salpingograms. Even then, the husband's sperm should be shown to be normal before operation is attempted.

There have recently been a number of optimistic reports on operations for tubal implantation and salpingostomy using polyethylene bougies to maintain patency, but it is also known that there are numerous errors in evaluation of the patency of tubes by air insufflation or oil injection. Many patients have been told that their tubes were closed, yet later they have been found patent by repetition of the tests or by the advent of pregnancy.

Suspension operations on the uterus are not indicated for the correction of infertility unless the fundus is fixed in retroversion by old inflammation or endometriosis, and even then it is likely that correction of the basic cause of the retroversion will be the deciding factor if pregnancy ensues. Mobile retroversions can almost always be corrected adequately if necessary, by the use of a reposition pessary. There is a rare exception to this rule, where a pessary cannot be maintained in position or where it does not rectify the displacement and all the above infertility tests are negative.

We have all had cases where multiple myomectomy has been followed by pregnancy. Fibroids may have some direct bearing on infertility, or it may be that the adventure of an operation has in some way shaken loose the patient's inhibitions or her endocrines so as to make pregnancy possible. It is well known that endometrial polyps very often accompany the fibroid uterus, and in many instances removal of these by curettage without myomectomy will be followed by pregnancy.

Apart from sterility, operation for fibroids is only indicated when there is a growing tumour in a uterus the size of a three-months' pregnancy or larger or when symptoms of marked pressure develop, or pain due to degeneration. Excessive bleeding is also an indication, but as this may be due to co-existing endometrial

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polyps and/or malignant tumour, curettage should always be done first and may obviate laparotomy in the smaller fibroid uterus, or indicate more radical treatment.

In younger patients, the uterus should of course be preserved, with removal of fibroids through as few incisions as possible and with meticulous elimination of raw surfaces. In older women whose families are complete, total hysterectomy is preferable. At the menopause or later, any uterus increasing in size, particularly if it is doing so rapidly, should be removed at once because of the possibility of sarcomatous change.

#### CANCER OF THE CORPUS UTERI

In early cases as estimated by duration of signs or symptoms, pelvic findings, and curettage, total hysterectomy with bilateral salpingo-oophorectomy will probably give as good a cure rate as any other method of management, particularly if done immediately upon finding cancer tissue at the first curettage. If this treatment is decided upon, the cervix should be closed and the tubes ligated to prevent spill during operation, and radium applied to the vaginal vault after operation.

It seems to be generally agreed, however, that if radium is available for insertion at the first curettage, it should be used and followed up by surgical removal of the uterus, tubes and ovaries in six to eight weeks. This is the best treatment in cases which are not apparently early ones. In the literature today there appear to be an increasing number of advocates of radical hysterectomy and pelvic lymphadenectomy in the more advanced cases of cancer of the corpus uteri. One might be inclined to agree with this procedure if a reasonably early malignant tumour encroaches upon the endocervix, indicating a lymphatic spread to the obturator, hypogastric and iliac lymph nodes, as is usual in primary cancer of the cervix.

In the more advanced cases of cancer high in the fundus however, metastatic spread is much more likely to be to the lumbar and aortic nodes and the usual type of pelvic lymphadenectomy would be useless. Furthermore, as cancer of the corpus occurs frequently in older women and is often associated with obesity, diabetes or high blood pressure, many cases might have to be ruled out as poor risks for radical operation.

#### PBE-INVASIVE CANCER OF THE CERVIX

If the lesion has been completely removed by cone biopsy and dilatation and curettage from a young woman desirous of pregnancy, it is probably justifiable to continue observation with frequent cytological studies. This plan, however, must presuppose that the most careful multiple serial sections have been taken and studied to rule out any evidence of invasion. Use of Schiller's iodine test will mark the extent of the lesion on the portio or on to the vaginal fornices, so that removal at biopsy may be complete. In the older patient, where pregnancy is not a consideration, we feel safer in removing the uterus with a good vaginal cuff even though the pre-invasive lesion has been completely removed by biopsy. The ovaries and tubes may be left. That conservative treatment is correct remains to be proven.

#### INVASIVE CANCER OF THE CERVIX

At the present time, the treatment of choice in all stages, I to IV, is primarily radium application to the uterus and upper vagina, with x-ray or the cobalt bomb to the pelvic lymph node regions. In stages I and II and the occasional case in stage III, if the cancer is resistant to radium attack as evidenced by continuing positive cytology or biopsy, unusual sloughing, parametrial extension or inexplicable loss of weight, radical abdominal hysterectomy with pelvic lymphadenectomy in surgically suitable cases may offer the patient a chance of cure of an otherwise hopeless condition. However, in these radium-resistant cancers surgical results are poor also, possibly because the disease is more virulent or host resistance is poor, with increased involvement of lymph nodes.

Work being done now by Ruth Graham on cytological studies to determine cell sensitivity and radiation response may offer an opportunity to use operation alone and earlier with the hope of some slight improvement in salvage. Radical operation, like radium, is not the answer to treatment of cancer here or elsewhere. Even with the most meticulous and careful dissection, clean block removal of *all* involved tissue is not possible in *any* case. Lymph channels are disrupted and dissemination of the disease is always a possibility. In the hands of the most experienced operating teams in the world mortality rates to date can be improved only slightly by operation. In the meantime much harm may

be done and many lives lost by an overenthusiastic surgical attack by men of lesser ability and experience. If there is to be any advantage to the patient from operation in these cases, it should be performed only by operating teams with the best training possible, prepared to do the most extensive procedures meticulously, and able to handle any emergency. In 20-25% of all cases of metastases to pelvic lymph nodes pararectal nodes are involved, and if one is unprepared to remove all possibly involved tissues, one probably should not treat these cases surgically at all. This applies also to the super-radical operations of exenteration, total or partial, in cases of recurrent cancer of the cervix. Central recurrence with extension to bladder or rectum of limited degree is probably the only instance where this operation is indicated.

George Crile, Jr.<sup>2</sup> has stated that: "In some of our specialized hospitals along with the practice of ultra-radical surgery, there has developed a philosophy that the presence of cancer justifies anything that the surgeon elects to do. Useless operations on the uterus or appendix would not be tolerated at these hospitals, but useless operations on cancer are accepted without question. Surgeons deeply imbued with the doctrine of ultra-radical surgery refuse to recognize that certain cancers cannot be helped by operation even when these cancers have been documented as inoperable. These surgeons do not admit that their attempts to cure usually do harm. The consistent failure of ultra-radical operations to arrest advanced cancers of high malignancy, the devastating side effects of these operations, and their high cost are shaking the faith of patients and physicians in the surgery of cancer. The radical attack should be pressed only in those fields where it gives promise of success." While this criticism sounds a bit harsh, it probably does apply in some instances.

#### CANCER OF THE CERVIX COMPLICATING PREGNANCY

Ideally, vaginal and cervical cytology should be studied on every woman but particularly on all pregnant women when first seen; if indicated, adequate biopsy specimens should be taken from any presenting lesion. If there is no visible lesion, or if a small biopsy specimen is negative but cytology suggests malignancy, cone biopsy should be done. Pre-invasive cancer may then be followed up by study of smears throughout pregnancy, and it is probably safe to do this even if all the lesion has not been removed from the upper cervical canal. We have

not seen invasive cancer above the cone biopsy when the remainder of the lesion is intraepithelial. There is room for individualization of cases here of course.

In early pregnancy, invasive cancer of the cervix is at present treated by radium and x-rays with or without emptying of the uterus. In later pregnancy the uterus should be emptied by Cæsarean section when the fetus is viable, and x-ray treatments begun and radium inserted later when involution is complete. There may be some advantage in this instance, however, in performing radical hysterectomy and pelvic lymphadenectomy at the time of Cæsarean section, thus avoiding delay in definitive treatment. Ultimate clarification of classification of cancers as radium resistant or sensitive will no doubt have an effect on the proper choice of treatment in these cases.

#### CANCER OF THE VULVA

Simple vulvectomy is indicated in pre-invasive cancers as in leukoplakia.

Invasive cancer here is probably best treated by wide excision of the vulva to the periosteum with removal of all inguinal, femoral, femoral canal, obturator, hypogastric and iliac lymph nodes bilaterally. In favourable locations and with an early lesion, or a poor-risk patient, one might remove the nodes on one side only and do no more if they are found to be uninvolved. Admittedly this is taking a slight chance, and should not be the procedure of choice in lesions of the anterior vulva or clitoral region. In other cases a two-stage or three-stage operation may be advisable or node dissection may be done on both sides simultaneously. Cancers of the lower anterior or posterior vagina are poor choices for surgical treatment because of technical difficulties and lymphatic spread, and unless extremely early, are better treated with radium.

#### OOPHORECTOMY

In general, simple cysts, endometriosis, and benign dermoids or proliferative cysts of the ovaries should in young women be treated conservatively by excision of abnormal tissue and saving of all normal tissue possible. The presence at operation of a pathologist who can collaborate in diagnosis of gross specimens or frozen sections will sometimes save an ovary if not



both ovaries and a uterus. In tumours such as the granulosa cell, dysgerminoma, and arrhenoblastoma, it may also be possible to preserve the child-bearing function.

One tends to be less conservative when the patient is a woman approaching 40 who has satisfied her maternal instincts. Solid tumours and proliferative cystic tumours, benign or malignant, are usually treated by removal of both ovaries, tubes, and the whole uterus, because of the occasional difficulty in deciding even histologically between the benign and the malignant. If cancer is found in one ovary, the risk of metastases to the other ovary or to the uterus is too great to leave them behind. The abdomen should also always be explored carefully for metastases, for a primary mother tumour with the ovarian cancer secondary, or for a separate primary tumour.

The finding of advanced cancer of the ovary with metastases indicates the removal of as much of the original tumour and metastases as is possible. In deep pelvic involvement it may be wise in certain cases to leave the uterus in, so that subsequent radiation treatment may be enhanced by intra-uterine radium.

Cystic enlargements of the ovary up to the size of a lemon and solid enlargements of half that size should be observed at monthly intervals for evidence of growth; if they increase in size or become fixed, they should be investigated by laparotomy. In postmenopausal women even earlier interference is justifiable.

A word about so-called prophylactic oophorectomy. The average age for the menopause in this country is 47. Ovarian function is altered but does not cease with the menopause. Severe menopausal symptoms occasionally occur when the ovaries are removed years after menstruation has stopped. According to Metropolitan Life Insurance Company figures, the incidence of ovarian carcinoma for women over 50 years of age is 37.3 per 100,000. This means that the best we can do by removing normal ovaries during laparotomy for other benign conditions is to prevent cancer in three out of 10,000 patients. If we remove ovaries routinely at the age of 45 or younger, as some writers suggest, we will plunge thousands of women into a surgical menopause. For many of these women this would be bad. We feel that in this problem, individual assessment should play a strong part. A bad family history or fear of cancer might

indicate earlier removal of ovaries, while in the patient who is emotionally unstable or fears loss of sex, the indication might well be to leave them alone. As a general rule, we would probably be right in removing ovaries prophylactically at age 50 and no less.

#### PELVIC INFLAMMATORY DISEASE

In younger patients with chronic pelvic infection of any nature, conservative therapy should be given an exhaustive trial and should consist of bed rest, antibiotics, and heat over a period of months. If recurrences are attended by repeated failure to cure, and illness and pain are interfering with a happy existence or the ability to earn a living, then only should surgical relief be attempted. With antibiotics and chemotherapy, these cases are fortunately rare; where the disease process is progressive, genital tuberculosis should always be suspected. When the case merits surgical intervention nowadays, anything less than excision of all diseased tissues together with removal of the uterus is likely to mean further operation in the future.

In older patients who have had their family, prolonged conservative therapy does not merit the same consideration.

The medical treatment of genital tuberculosis has improved with the advent of streptomycin, isoniazid, etc., but so far complete cures are unlikely. If the tubes are closed, they will not reopen and pregnancy, even if it could occur, would be considered inadvisable in the presence of tuberculosis of the uterus, tube or ovary. The surgical indication still is removal of both tubes and the uterus, and ovaries if they appear grossly involved.

#### PELVIC ENDOMETRIOSIS

The diagnosis of endometriosis is not in itself an indication for surgical treatment. If, however, an obvious endometriosis is causing increasing pelvic intermenstrual pain and/or dysmenorrhœa which conservative therapy fails to alleviate, surgical intervention may be called for. If the patient is young and married, pregnancy should be encouraged as it may relieve her complaints. If pregnancy does not occur within a reasonable length of time, the usual sterility tests should be done — sperm test, Hühner's postcoital test, and a Rubin test or a salpingogram. If these are normal, a conserva-



tive operation may be undertaken where ovaries are freed from adhesions and abnormal tissue removed from them. Tubes may also be freed from adhesions and straightened and endometriomatous implants removed, and possibly a uterus fixed in retroversion may be freed and suspended.

Operation should never be attempted if an asymptomatic endometriosis is found during investigation of infertility until sterility tests have been done.

In the patient 40 years of age or over, who has had her family and who is suffering increasing pain as a result of endometriosis, more radical surgery may be indicated. Unless one can be sure that removal of endometriomatous cysts and implants will relieve her symptoms, it is better to take out all the abnormal tissue possible and the ovaries or, better still, the uterus, tubes and ovaries. Results of radium or x-ray treatment of this condition are not as good as those of surgery, and high prolonged oestrogen dosage usually affords only temporary relief — and may be dangerous.

#### VAGINAL REPAIR AND VAGINAL HYSTERECTOMY

In young women up to 35 years of age who want children and who have a degree of vaginal relaxation which with accompanying symptoms demands repair, really conservative surgery is indicated. Cystocele and rectocele should be repaired, but the cervix should be left alone unless it is grossly infected or markedly hypertrophied or elongated. Even then, cauterization or light conization or superficial amputation should be the maximum of interference.

Between the ages of 35 and 40 there may be a place for the Fothergill or Manchester type of operation, but even then high cervical amputation should be avoided in the interest of possible childbearing. Prolapse can be cured without high amputation of the cervix, or even without amputation at all, but of course a greatly elongated cervix will have to be shortened.

In the woman of 40 years and over, we feel that any indicated repair of the vagina should be accompanied by vaginal removal of the uterus, provided of course that she does not wish to utilize it further for childbearing, and also provided that it can be removed without increased risk. Vaginal hysterectomy with proper vaginal repair does require more effort from the surgeon, but if it is advantageous

to the patient we should be willing to expend this effort. The advantages to the patient are:

1. It removes the fear of pregnancy at an age when this is usually most undesirable, and when such fear may cause serious rifts in marital relations.

2. It removes the possibility of pregnancy, which might break down the vaginal repair or necessitate Cæsarean section as an alternative.

3. It prevents the sometimes serious bleeding during the menopausal years, and the worry of missed periods or intermenstrual bleeding. It therefore also prevents the possible necessity of later hysterectomy, or diagnostic operation.

4. The miserable and now quite fashionable syndrome of premenstrual tension is usually completely relieved, and dysmenorrhœa becomes a nightmare of the past.

5. It affords an opportunity to inspect the ovaries and tubes and in many instances to remove them if indicated.

6. Last but not least, it precludes the possibility of cancer in any part of the uterus.

The above advantages apply to the prophylactic removal of the uterus during vaginal repair. When abnormal bleeding or other disease in the uterus indicates its removal, there are other distinct advantages to vaginal hysterectomy as opposed to vaginal repair plus abdominal hysterectomy: (1) less pain; (2) less disfigurement; (3) less chance of damage to ureters; (4) less risk for the patient; (5) a more rapid convalescence.

Falk and associates<sup>10</sup> reporting on incidental lesions in vaginal hysterectomy for uterine prolapse found that, out of 174 patients who had no other complaint than prolapse and on examination no evident uterine or adnexal abnormality, 114 (65.5%) showed definite uterine or adnexal lesion. They feel that some of these patients might have required further operation if the uterus and abnormal adnexa had not been removed.

There are a few indications which should be kept in mind when doing vaginal hysterectomy with vaginal repair:

1. Vaginal, cervical, and intrauterine cytology should be studied a week or more preoperatively.

2. Curettage should be done as a preliminary step to operation or the uterus should be opened on its removal to expose a possibly malignant tumour of the corpus.

3. Although large fibroid uteri can be removed by morcellation, a previous history of severe infection or pelvic findings of advanced endometriosis, large ovarian cysts, or operations such as ventrofixation of the uterus, should influence one against vaginal hysterectomy.

4. Careful reconstruction of the vaginal vault is essential to avoid vault prolapse.

5. In almost 100% of women who have borne children and in whom repair is necessary, the posterior vaginal repair should be carried to the vault to avoid later enterocele or high rectocele. This is true of ordinary vaginal repair work too, as is the routine plication of the bladder neck whether urinary incontinence was a preoperative symptom or not.

We do not feel that there is any indication today for vaginal repair plus abdominal uterine suspension or fixation in the cure of prolapse. There certainly are indications for vaginal repair with abdominal hysterectomy or other intra-abdominal procedures which cannot properly be carried out per vaginam.

We do not feel that there should be any indication for Watkin's interposition operation, the Spalding-Richardson operation, or the Le Fort operation. The first and last leave the uterus in an invidious position, and the other accomplishes less than does vaginal hysterectomy and yet is a more involved procedure.

Obviously, as we mentioned at the beginning of this paper, the training and experience of the gynecologist will influence his choice of operation regardless of indications.

We do not wish to condemn the Manchester type of operation but as most instances of vaginal or uterine prolapse requiring operation occur in women beyond the childbearing age, or with all the children they want, we feel that in the hands of well-trained gynecologists vaginal hysterectomy with complete vaginal repair is a definitely superior operative procedure. It provides equal anatomical and better clinical results.

One final general indication should be mentioned. If laparotomy is decided upon for benign pelvic disease, relaxation of the vagina should never be overlooked. If this principle is followed, many patients will be saved the additional risk and expense of later reparative surgery. If it is not feasible to carry out the necessary surgery vaginally, it is better to do the vaginal repair first and follow with laparotomy.

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#### RÉSUMÉ

Le gynécologue et sa patiente doivent s'entendre pour adopter une attitude aussi conservatrice que possible à l'égard des interventions majeures pour la correction de l'infertilité, de même que pour toute autre opération pendant la période productive de la vie génitale. On doit chercher à prévenir le cancer des voies génitales de la femme avant qu'il n'atteigne un stage où le traitement radical s'impose, par le dépistage précoce des néoplasmes au moyen des épreuves de laboratoire que nous avons maintenant à notre disposition, et dont la précision augmente constamment. Il importe que toutes les femmes se soumettent à ces épreuves à des intervalles annuels ou bi-annuels. Pour en arriver à ces fins, il est nécessaire d'éveiller l'attention du grand public pour en obtenir la collaboration. Lorsque ces facilités de laboratoire dont nous disposons permettront l'examen cytologique vaginal de toute la population féminine une fois par année, et lorsque nous pourrions persuader ces femmes de se présenter à ces examens, il est probable que les formes les plus fréquentes de cancer des voies génitales de la femme pourront être complètement éliminées. Lorsqu'on doit pratiquer une forme quelconque de chirurgie pelvienne, vers la fin de la période sexuelle productive pour fixation ou autre intervention, il faut toujours songer à enlever les organes qui n'ont plus de fonction utile et qui par contre peuvent devenir le point de départ de cancers futurs.

#### A NEW APPROACH TO THE PHYSIOLOGY OF SO-CALLED "CARDIOSPASM"

Achalasia must not be isolated as a special disease of the cardia. Local stenosis and proximal dilatation may appear in other segments of the digestive tract, the result of a similar anomaly of Auerbach's plexus. Hirschsprung's disease, achalasia of the pylorus, mega-jejunum and mega-ileum are examples. The contraction of the circular musculature may occur in other than sphincter regions.

Experimental production of cardiospasm in cats by the destruction of Auerbach's plexus by local injection of phenic acid into the oesophageal wall was undertaken at Brussels. Phenic acid destroys nervous cells without necrosis of other structures. It was shown that megaesophagus develops after cardiac stenosis clinically, anatomically and radiologically. The stenosis at the lower end of the oesophagus persisted at post-mortem in the removed specimens. Microscopic examination showed lesions typical of the human disease: destruction of the ganglion cells of Auerbach's plexus.—L. Deloyers, R. Cordier and A. Duprez: *Ann. Surg.*, 146: 167, 1957.



# THE CLINICAL COURSE OF ACUTE RENAL FAILURE OBSERVATIONS ON 54 CASES\*

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THE MANAGEMENT of 54 cases of acute renal failure seen since 1947, together with a plan of treatment, has been reported previously.<sup>1</sup> The importance of blood dialysis in selected cases was emphasized. In this paper we wish to summarize our observations on the clinical features of the syndrome. The main findings in the individual cases have been tabulated in the earlier communication.<sup>1</sup>

## PATHOGENESIS

The various etiological factors are shown in Table I.

TABLE I.—CLINICAL ETIOLOGY, ACUTE RENAL FAILURE (54 Cases)

	No. of cases	Totals
I. <i>Ischæmic Nephrosis</i>		
Obstetrical complications.....	19	
"Septic" abortion.....	9	
Eclampsia.....	4	
"Spontaneous" abortion.....	3	
Abruptio placentæ.....	2	
Post-partum hæmorrhage.....	1	
"Surgical" shock.....	8	
Crushing injury.....	6	
Transfusion reactions.....	2	
Cardiac tamponade, post-commissurotomy.....	1	
Retrograde pyelography.....	1	37
II. <i>Nephrotoxic Nephrosis</i>		
Carbon tetrachloride.....	8	
Alcoholism (acute).....	3	
Mercuric chloride.....	2	
Mushrooms.....	1	
Fluoride.....	1	
Unknown.....	1	16
III. <i>Acute Nephritis</i> .....	1	

## A. *Ischæmic Nephrosis*:

This group includes over two-thirds of the cases and it will be noted that the majority of cases followed obstetrical complications, major abdominal surgery and severe crushing injury. Our observations suggest that surgical shock rather than hæmolysis was the main pathogenic factor.

(a) *Shock*.—Surgical shock was directly observed, or presumed from the history, in all cases and it is believed that this resulted in severe renal ischæmia. Whether the ischæmia is due simply to the effects of prolonged hypotension, or whether selective renal vascular reflexes secondary to regional and distant trauma participate, is unknown. In Case 1 reflex ischæmia was a probable factor. Direct trauma to renal areas was observed in only a few of the crush cases, and therefore renal contusion is believed to be a relatively unimportant factor.

(b) *Hæmolysis*.—Review of our cases did not show clearly that hæmolysis alone was sufficient to produce acute renal failure. Acute hæmolysis was due to (1) hæmolytic infection in septic abortion (Cases 32, 49, 50, 54) and (2) transfusion reaction (Cases 10, 33). As far as can be determined from the records hæmolysis was invariably accompanied by hypotensive shock. All our cases were seen after the onset of acute renal failure, frequently several days after, and in emergencies sometimes recorded clinical data were inconclusive.

Transfusion reaction (hæmolysis plus shock) was recognized in only the two instances, although all cases in the ischæmic group, except Case 1, received one or more blood transfusions. In seriously injured or unconscious patients, the occurrence of reactions may be overlooked. However, with one exception (Case 33), all blood was provided by the Canadian Red Cross and was carefully selected and cross-matched, apart from the emergency use of Group O blood on several occasions. In a number of instances after the onset of acute renal failure, it was possible to recheck cross-matching without demonstrating evidence of incompatibility. In at least four cases (Cases 1, 14, 23, 24) transfusion either was not given before the onset of renal failure or was sufficiently remote to be excluded as a cause. We believe therefore that there were few if any instances of unrecognized transfusion reaction, and it is our opinion that, as an isolated factor, hæmolysis was not a cause of acute nephrosis in any of the cases.

Our observations are in accord with the experimental work of Maluf,<sup>2</sup> who demonstrated in dogs that hæmoglobinæmia produced acute renal failure only when combined with a low rate of glomerular filtration (e.g., due to shock, dehydration).

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### B. Toxic Nephrosis:

In this group the renal injury is due to a protoplasmic poison which has predominant effects on the proximal tubules.

Carbon tetrachloride was the leading cause of morbidity in our cases. In all instances, the carbon tetrachloride was ingested or inhaled accidentally. In five instances this occurred while the material was being used as a cleanser or solvent, again emphasizing the domestic and industrial hazards of this agent. Coincident hepatic degeneration was recognized in six of the eight cases.

In three cases severe acute alcoholism, usually of more than a week's duration, was the only evident and therefore the presumed cause. A toxic agent was presumed in Case 28; the patient received streptomycin and PAS for localized pulmonary tuberculosis and exhibited thermal, dermal and other general manifestations of severe toxicity a few days before the onset of acute renal failure.

### DIAGNOSIS

With few exceptions (Case 1), acute renal failure was secondary to severe extrarenal injury or intoxication. Because of this its onset was overlooked for a time in several cases, in the preoccupation with the precipitating cause. However, it was recognized promptly when basic observations of body functions were being made, and when the possibility of the complications was kept in mind.

Differentiations from acute obstruction rarely presented serious difficulty. Acute obstruction of both renal tracts rarely occurs above the bladder neck (e.g. pelvic injuries, bladder tumour, renal pelvic crystal deposits), and for this reason catheterization of the bladder was usually sufficient to exclude obstruction. When doubt remained, retrograde catheterization of the upper urinary tract was done.

Acute glomerulonephritis rarely begins with oliguria of sufficient severity and duration to resemble acute nephrosis, Case 38 being an example. Differentiation depended on the presence of clinical features of acute glomerulonephritis, and the absence of a precipitating cause for acute nephrosis. As noted below, the recovery pattern was also different.

The uræmia of terminal chronic renal disease can be recognized, usually, on clinical grounds. Retinopathy commonly present in chronic disease

was not encountered in acute nephrosis, with the exception of arterial spasm in eclampsia.

### CLINICAL COURSE

#### I. Stage of Onset:

This was managed elsewhere in all cases and will not be discussed in this paper. Precipitating causes are presented in Table I.

#### II. Oliguric Phase:

*Urine output.*—The characteristic clinical feature of all cases was the severe oliguria persisting for one, two or more weeks. In a few cases this was a virtual anuria, but in 42 cases the 24-hour urine volume varied up to 200 ml. and in 11 cases 24-hour volumes up to 600 ml. were observed. When examined in the first 48 hours the urine in the ischæmic group usually contained altered hæmoglobin pigment. Thereafter small quantities of protein and a variety of cellular debris were found, and the specific gravity was low.

*Water balance.*—Because of the practical difficulties of maintaining water balance, overhydration was present in a majority of the cases. This varied from a general appearance of slight puffiness to frank pitting œdema in the legs and flanks. Cases managed elsewhere early in the oliguric phase, on fluid intakes which were too liberal, exhibited the most marked states of overhydration. Under conditions of strict water control it was always possible to prevent weight gain, and even induce a limited weight loss during the oliguric phase (Fig. 1). However, even when conditions of water balance appeared to be ideal, resulting in a steady weight status or a slight loss, undoubtedly water was being retained, replacing tissue. This was illustrated by the invariable loss of considerable weight during the diuretic phase, as noted below, and may account for the fact that pulmonary œdema occurred frequently in the absence of other evidence of overhydration (Table II in the preceding paper).

*Cerebral status.*—Somewhat over 50% of all patients had symptoms of cerebral disturbances such as irritability, restlessness, confusion, semi-coma, and coma, and convulsions, usually appearing late in the oliguric phase. Overhydration may have contributed to this. Of 27 patients with some clinical sign of overhydration seven had convulsions, whereas in 21 cases without clinical evidence of overhydration there were no convulsions.

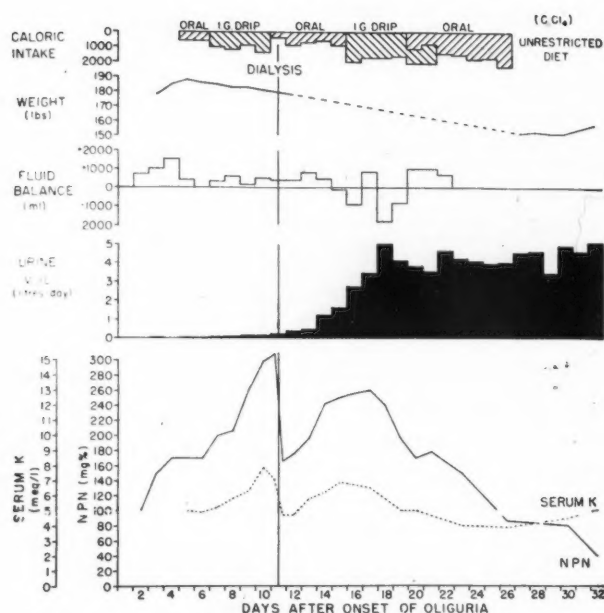


Fig. 1.—Case 44: White male, aged 51.  $\text{CCl}_4$  poisoning. (a) Overhydration despite limitation of fluid intake. (b) The efficacy of intragastric drip (I.G.) feedings. (c) The rapid stepwise expansion of the diuresis beginning at the end of the second week. (d) The biochemical lag after the onset of diuresis. (e) The effect of the dialysis.

**Circulatory status.**—Most cases had a mild or moderate tachycardia, while two cases (27 and 47) had ventricular tachycardia, which was a terminal manifestation in the former. Less than 50% developed mild or moderate hypertension (140/90 mm. Hg or over). This could not be related definitely to the degree of clinical hydration. However, the development of hypertension appeared to predispose somewhat to pulmonary congestion, which developed in 75% of the "hypertensive" group and in less than 50% of the normotensive group. The normotensive and hypertensive groups showed no important difference in cerebral status.

**Anæmia.**—Hæmoglobin values are summarized in Fig. 2, which separates the ischæmic and

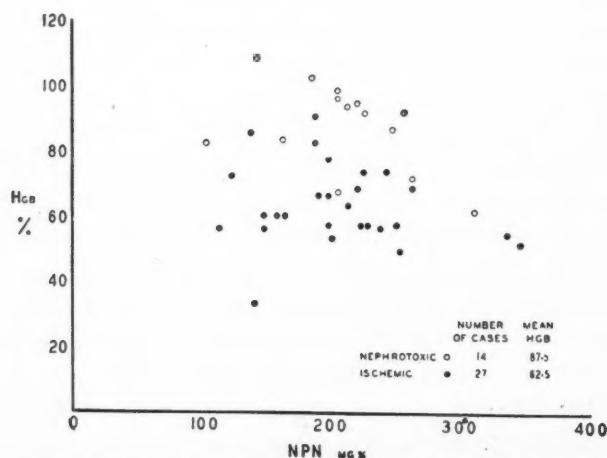


Fig. 2.—Hæmoglobin values at the height of azotæmia.

toxic cases. Non-protein nitrogen (NPN) is shown as the highest value available within 24 hours of a hæmoglobin determination. In most cases it represents the height of the azotæmia. It is to be noted that anæmia is more severe in the ischæmic group, suggesting a predominant extrarenal cause, probably blood loss, or in a few cases hæmolysis. Hæmoglobin trends have been plotted for the nephrotoxic group in Fig. 3, excluding those cases in which the hæmoglobin was affected by hæmodialysis. With few exceptions there was a progressive deterioration, indicating that factors other than blood loss contribute to the anæmia of acute renal failure. Possible factors include toxic depression of bone marrow and reduction of the erythrocyte life span. The rate of hæmoglobin decline in most cases would be compatible with suppression of the bone marrow activity. Uræmic suppression of bone marrow is suggested also by the consistent failure of the anæmia to respond to hæmatinics.

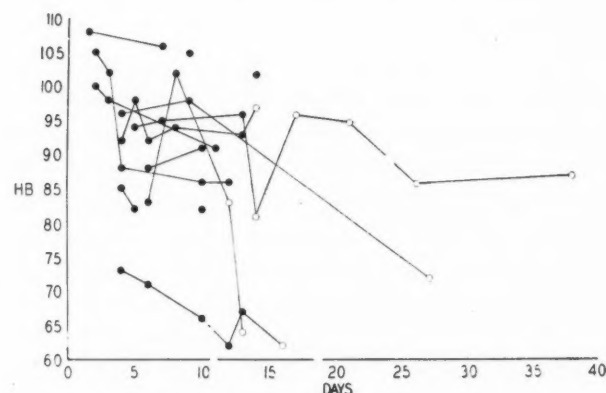


Fig. 3.—Toxic nephrosis. Open circles indicate beginning decline in the azotæmia.

**Azotæmia.**—Usually the blood NPN was an index of the severity of the uræmia, but in individual cases it was sometimes unreliable. Thus, of 11 patients with a blood NPN peak less than 200 mg. %, seven had alterations of cerebral status and six had pulmonary œdema, whereas of 19 patients with blood NPN greater than 200 mg. % seven had alterations of cerebral status and nine had pulmonary œdema.

**Electrolytes.**—Electrolyte disturbances for nine cases are summarized in Fig. 4 which demonstrates mild sodium, chloride, and bicarbonate depression and potassium retention in the oliguric phase, later corrected in the phase of recovery. As noted below, we rarely encountered serious electrolyte depletion in the diuretic phase.

TABLE II.—CASES EXHIBITING HYPERKALÆMIA

Case No.	Precipitating injury	Severity of injury	Hæmolysis (gross)	Serum potassium mEq./l.	Comments
<b>A. Ischæmic Nephrosis</b>					
<i>Crush injury</i>					
17	Crush	Extensive injury to lower trunk and perforation of bowel	Not obs.	12.8	Died D2 as a result of hyperkalæmia before dialysis could be arranged
47	Crush	Extensive multiple fractures and ruptured kidney	0	11.0	Hyperkalæmia controlled by dialysis, but death occurred D6, due to extensive injuries
20	Crush	(R) thigh and lumbar psoas	0	7.7	Hyperkalæmia relieved by spontaneous diuresis but died D20 from other causes
25	Crush	(L) arm and shoulder and concussion	0	7.5	Hyperkalæmia relieved by dialysis but died D4 from injuries
<i>Transfusion Reaction</i>					
10	Uneventful operation for scalenus syndrome		+	8.2	Successful treatment by dialysis
<i>Obstetrical Complications</i>					
23	Eclampsia	Severe cerebral, hepatic and renal involvement	Nil	10.0	Hyperkalæmia relieved by 3-hour dialysis D13; recovery
19	Postpartum hæmorrhage	—	Not obs.	8.9	Received 6 bottles of blood. Recovered spontaneously. Potassium depletion in diuretic phase
30	Eclampsia	Renal cortical necrosis	Not obs.	8.9	Severe uræmic toxicity
35	Abruptio placenta	—	Presumed (icteric)	7.5	Died at end of dialysis
18	Ruptured ectopic pregnancy	—	+	7.0	Died D8 awaiting dialysis. Received 8½ bottles blood
46	Spontaneous abortion	—	?	6.6	Auto-transfusion with blood recovered from peritoneal cavity. Died D14
36	Spontaneous abortion	—	+	6.5	Treated successfully by ion exchange resins
54	Septic abortion	—	Icterus +++++	6.3	Received 6 pints of blood
51	Septic abortion	—	Not obs.	5.8	Recovery
50	Septic abortion	—	+++ (infection)	5.7	Hæmolytic infection presumed. Received 13 bottles blood. Died D4
52	Spontaneous abortion	—	Not obs.	5.6	Dialysis effective biochemically but died following day (D11)
29	Septic abortion	—	?	5.6	B. welchii infection (presumed). Recovered
<i>Postoperative Surgical</i>					
13	Appendicitis	—	Not obs.	6.5	Tube feeding effective
34	Gastrectomy, post-operative shock	—	0	5.8	Dialysis effective biochemically but died following day
<b>B. Toxic Nephrosis</b>					
28	Unknown (PAS)	—	—	8.2	Died as a result of severe uræmic toxicity
44	CCl <sub>4</sub>	—	—	7.9	Recovered without specific therapy
					Recovered; dialysis effective; subsequent hyperkalæmia treated effectively with resins



TABLE II.—(Continued)

Case No.	Precipitating injury	Severity of injury	Hæmolysis (gross)	Serum potassium mEq./l.	Comments
40	Alcohol	—	—	7.0	Recovery
53	Alcohol	—	—	6.6	Died D12 mainly due to pulmonary oedema
48	CCl <sub>4</sub>	—	—	6.2	Recovered
41	CCl <sub>4</sub>	—	—	6.2	Died D13 due to pulmonary oedema and ventricular tachycardia
45	CCl <sub>4</sub>	—	—	6.0	Recovered
27	CCl <sub>4</sub>	—	—	6.0	Died due to uræmic toxicity D12
22	CCl <sub>4</sub>	—	—	5.7	Recovered
42	Alcohol	—	—	5.6	Recovered; ion exchange resin reduced serum K
43	Mushrooms	—	—	5.1	Recovered

Serum potassium abnormalities are also summarized in Table II, which shows all cases with elevated potassium values ( $>5$  mEq./l.). Thirty-one of the 54 cases had some degree of hyperkalæmia. The two highest values occurred in cases of severe generalized crushing injury (Cases 17 and 47), and only in the former was it the main cause of death. Otherwise severe hyperkalæmia was not related to the

etiological agent or to the duration of the renal failure. Apart from the crush injuries the highest potassium value was observed in eclampsia (Case 23). Hyperkalæmia, of mild to moderate severity (5.7-8.2 mEq./l.), was observed in three (Cases 10, 50, 54) of the six cases (Cases 10, 32, 33, 39, 50, 54) in which there was recognized acute hæmolysis (see Table II in preceding paper).<sup>1</sup>

As a rule the electrocardiogram was an unreliable index of the severity or trend of the serum potassium abnormality. This may be due to the effects of other electrolyte abnormalities, principally the calcium ion, as noted by Meroney and Herndon.<sup>3</sup>

*Other features.*—All patients had anorexia, and the majority nausea and intermittent vomiting of small quantities, particularly in the latter half of the oliguric phase. One case showed a moderately severe fever ( $102-103^{\circ}$  F.) not due to other apparent cause, autopsy revealing no evidence of infection.

### III. Diuretic Phase:

The diuretic phase usually developed after a week or more of oliguria. Fig. 5 summarizes our experience in this regard. It is constructed after Stock,<sup>4</sup> the day of onset of diuresis being selected as the day in which 1000 ml. or more of urine was produced. The nephrotoxic cases displayed a more uniform timing of recovery, possibly because of a more uniform type of renal injury and less extensive extrarenal damage.

Diuresis developed rapidly in a step-wise pattern, in geometric progression in the course of five or six days from an output of 100-200

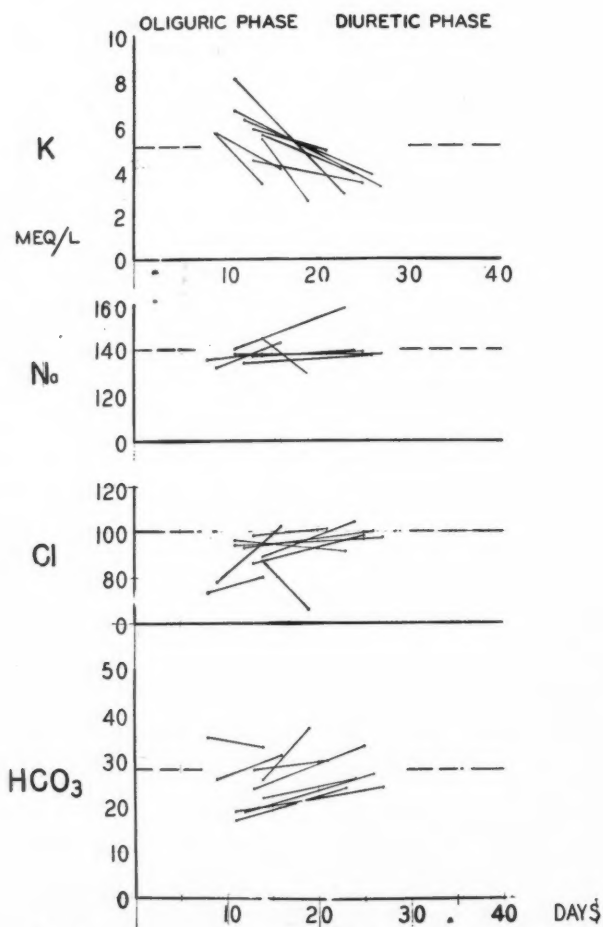


Fig. 4.—Serum electrolyte observations in nine cases.

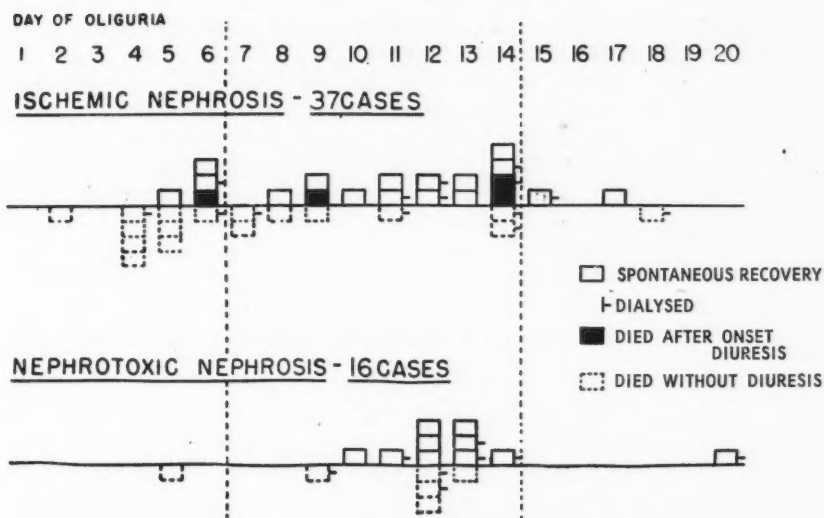


Fig. 5.—Onset of diuresis (>1000 ml./24 hours) in acute renal failure—53 cases.

ml. to 3000-4000 ml. each 24 hours. The typical pattern is illustrated in Fig. 1. It is to be contrasted with the pattern of recovery in acute nephritis (Fig. 6) which is much more gradual, the urine not attaining as large a daily volume. The urine is dilute, with a specific gravity of less than 1.010, contains a little protein, and gradually increases in concentration in the course of several months.

The blood NPN continues to rise for four or five days after the onset of diuresis, after which time the net balance between glomerular filtration and tubular reabsorption becomes favourably adjusted to permit adequate nitrogenous excretion. Whether the excretory fault in the oliguric phase is mainly one of reduced glomerular filtration or of increased and abnormal tubular reabsorption is still unknown. It is probably a combination of the two. A few of our observations on glomerular filtration rate (GFR), employing inulin and creatinine clearances, early in the onset of diuresis suggest a low rate of filtration, varying between two and eight times the total urine volume. However, measurements of GFR in the early recovery phase are probably unreliable, as there may be abnormal tubular reabsorption of the test material.

During the phase of diuresis, electrolyte depletion is one of

the expected hazards, due to impaired reabsorption of electrolytes by the injured tubules. However, this was rarely a problem in our series and our experience corresponds with that of Swan and Merrill.<sup>5</sup> Serious depletion of electrolytes was prevented by permitting dietary ingestion of sodium chloride and by oral supplements of potassium chloride. Usually it was not necessary to administer electrolytes intravenously (Case 19).

During the phase of diuresis there was a rapid clearing of all symptoms of uræmia, nausea

and anorexia being relatively persistent. While diuresis was becoming fully established, in the course of a week or somewhat less, there was consistently a considerable weight loss, even in those patients apparently maintained in satisfactory fluid balance during the oliguric phase (see Fig. 1). This suggests that during the phase of oliguria, even with apparently satisfactory water balance, tissue wasting masks abnormal water retention.

#### OUTCOME

The mortality for all the cases in this series was 50% and was worse in the ischæmic group, mainly because of the severity of associated

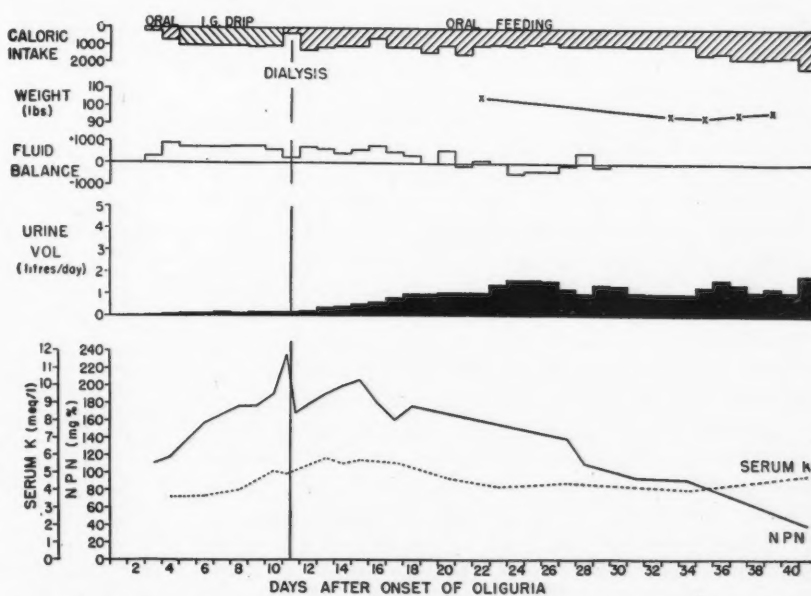


Fig. 6.—Case 38: White female, aged 15. Acute glomerulonephritis and diabetic acidosis. (a) The efficacy of intragastric (I.G.) drip feeding. (b) The gradual recovery in urine output. (c) The effect of the dialysis.



injury or disease.<sup>1</sup> In the nephrotoxic group, where the "injury" was predominantly renal, the mortality was 38% and the deaths were mainly due to extrarenal causes. Because extrarenal injury or toxicity will always be a serious factor in cases developing acute renal failure, it is suggested that an expected mortality in cases under ideal management for renal failure may be approximately 30-35%.

#### SUMMARY AND CONCLUSIONS

Fifty-four cases of acute renal failure have been reported in this paper, 53 being due to acute nephrosis (ischæmic and nephrotoxic), and one to acute glomerulonephritis. Approximately two-thirds of the cases were classified as ischæmic nephrosis and about half of these arose out of obstetrical complications. Approximately one-third of the total group are classified as nephrotoxic nephrosis, the main etiological factor being carbon tetrachloride. Acute alcoholism was an apparent cause in three of the cases.

In the ischæmic group hypotensive shock appeared to be an invariable precipitating feature, being either directly observed or presumed from the history of onset. Hæmolysis alone was a doubtful cause of acute nephrosis in our experience.

The most notable clinical feature was severe oliguria persisting for one or two weeks, occasionally longer. In approximately 75% of the cases the daily urine output was 200 ml. or less, but in the remainder the daily output was somewhat greater, occasionally up to 600 ml. a day in the oliguric phase. The next characteristic feature was azotæmia of progressive severity, with early and persistent gastro-intestinal manifestations and usually late cerebral manifestations. Cerebral disturbance was worse in overhydrated patients. Approximately 50% of cases developed a mild hypertension with a mild or moderate tachycardia, and two cases developed ventricular tachycardia.

Overhydration was probably present in all cases, but often it did not become manifest until restoration of the dry state in the phase of diuresis. Fifty per cent of the cases exhibited clinical evidence of overhydration, such as pulmonary oedema and/or peripheral oedema. Overhydration probably contributed to the symptomatic disturbance in all cases, but in our analysis a definite correlation could be established only in relation to the cerebral symptoms. It was our experience that overhydration was entirely due to errors of clinical management.

Anæmia was more severe, and observed more frequently, in the ischæmic group, probably because of blood loss or acute hæmolysis. However, other factors contribute to the anæmia of both groups.

Apart from hyperkalæmia, electrolyte disturbance was relatively mild. During the oliguric phase there was usually mild, occasionally moderately severe, hyponatræmia and a reduction in plasma bicarbonate and chloride. Hyperkalæmia of moderate severity

occurred in a number of the cases, being worse in those severely injured, but was a major cause of death in only one case. In our experience electrocardiographic abnormalities correlated poorly with the hyperkalæmia. During the phase of diuresis, electrolyte abnormalities became adjusted without specific therapy in most instances. Serious electrolyte depletion during this phase was uncommon, and it appears that severely injured tubules may retain or promptly regain the capacity to conserve electrolytes.

Functional recovery, featured by a rapidly expanding diuresis, usually began in the second week with a rapid remission in symptoms, gastro-intestinal disturbance being relatively persistent. The diuretic phase lasted for approximately a week, and was followed by a rapid recovery in the renal mechanism for controlling water balance. The azotæmia became worse in the first few days of the diuresis until excretory function became effective. Concentrating power recovered slowly in a period of months.

The mortality rate was 50%, and was worse in the ischæmic than in the nephrotoxic group.

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#### RÉSUMÉ

L'évolution clinique de l'insuffisance rénale aiguë est décrite ici dans ses grandes lignes d'après l'observation de 54 cas traités dans le département de médecine de l'hôpital général de Vancouver. Environ les deux-tiers de ces malades souffraient de néphrose ischémique alors que les autres montraient une atteinte néphrotoxique. Une période de choc sembla toujours faire partie intégrante du tableau clinique dans le groupe ischémique. Le fait clinique le plus important dans ces lésions est une phase oligurique qui peut durer jusqu'à deux semaines voire même plus longtemps. Celle-ci est accompagnée d'une azotémie d'intensité progressive avec son cortège de manifestations gastro-intestinales et cérébrales. Une hyperhydratation manifeste ou occulte sembla se retrouver dans chaque cas. Quelquefois on ne soupçonna sa présence qu'à la diurèse du début de la convalescence. Cette hyperhydratation provient toujours d'un traitement mal dirigé. L'anémie fut surtout remarquée dans le groupe ischémique. Le plus fréquent des déséquilibres électrolytiques fut l'hyperkaliémie. Il ne faut pas s'étonner d'une élévation temporaire de l'azotémie au début de la phase de diurèse. La mortalité de 50% de cette série fut plus marquée dans le groupe ischémique que dans le groupe néphrotoxique.

## THE SIGNIFICANCE OF AN APICAL SYSTOLIC MURMUR IN MITRAL STENOSIS\*

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THE POSSIBILITY of successful surgical treatment of tight mitral stenosis has brought back into discussion the problem of interpretation of the apical systolic murmur, which was already the subject of interesting debates in the nineteenth century.

Today, this problem is of more than theoretical importance, since its solution may have a practical and immediate significance. Evaluation of the systolic murmur is now, in our opinion, the most difficult problem in determination of operability.

The importance of this problem is two-fold. Firstly, the incidence of this murmur in cases of mitral stenosis is high. Janton, in his series, found an apical systolic murmur in 30% of cases of mitral stenosis. Froment states that almost 50% of his cases of mitral stenosis had a systolic murmur located between the apex of the heart and the xiphoid area. In our first 150 patients in whom mitral stenosis was confirmed at the time of operation, 48.7% had a systolic murmur in the apical region. Secondly, the presence of significant mitral regurgitation is an absolute contraindication to mitral commissurotomy.

Up to June 1, 1956, we had the opportunity of referring to our surgeons 258 patients for mitral commissurotomy. Only in three instances was the preoperative diagnosis of mitral stenosis not substantiated. In two cases, mitral insufficiency was predominant, and in the third case a thrombus partially obstructed a normal mitral orifice. The percentage of error is therefore 1.16%. In all the other cases, surgery confirmed the diagnosis of tight mitral stenosis, and enlargement of the mitral orifice was performed.

Since the beginning of our interest in mitral commissurotomy, it has appeared evident to us that a good number of apical systolic murmurs

do not indicate an insufficiency or a mitral regurgitation palpable by the exploring finger of the surgeon. We therefore felt that it would be interesting to review the auscultation findings in the first 150 patients operated on, in order to shed some light on the interpretation and significance of the apical systolic murmur in mitral stenosis.

We divided these murmurs in accordance with their intensity into four groups, following the usual method of classification employed at the Institute of Cardiology, as follows:

- Grade I—a murmur of low intensity.
- Grade II—a murmur of medium intensity.
- Grade III—a murmur of loud intensity.
- Grade IV—a murmur of very loud intensity.

### 1. *Systolic murmur of low intensity; Grade I.*

Out of 12 patients (16%) with an apical systolic murmur of low intensity, only one had a mitral regurgitation at the time of operation and the regurgitation was minimal. In six cases, its maximum loudness was at the apex and in the six others at the xiphoid process. In no case was transmission of the murmur to the axilla noted. In two cases, mitral calcifications had been observed, and this finding was confirmed at operation. The murmur in the only patient found to have regurgitation was loudest at the apex and did not radiate; the mitral valve was not calcified.

### 2. *Systolic murmur of medium intensity; Grade II.*

Out of 27 patients (37%) who had an apical systolic murmur of medium intensity, four had a regurgitation at the time of operation, three minimum and one moderate. The murmur was loudest in 14 cases at the apex, in seven cases at the inner side of the apex, and in six cases at the xiphoid process. The murmur radiated in four cases to the axilla and twice towards the xiphoid region. In 21 cases no transmission of the murmur was noted. In eight cases calcifications were found, and in 2 of these there was a regurgitation.

In the four cases where mitral insufficiency was found, the murmur was localized at the apex and twice it radiated towards the axilla.

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### 3. Systolic murmur of loud intensity; Grade III.

Out of 22 patients (30%) who had an apical systolic murmur of loud intensity, seven had at the time of operation mitral regurgitation (four minimum, one moderate and two considerable). In 13 cases the maximum intensity was at the apex, in two cases at the inner side of the apex

was maximal at the apex and in one at the xiphoid region. Only in one case did it radiate to the axilla.

Of 73 patients (48.7%) with an apical systolic murmur (Table I), 16 had mitral regurgitation at the time of operation. The maximum intensity of the murmur was at the apex in 39 cases, at the inner side of the apex in 10, and in the xi-

TABLE I.—MITRAL STENOSIS WITH APICAL SYSTOLIC MURMUR

Grade	No.	Localization			Radiation			Calcification	Regurgitation		
		Apex	Between	Xiphoid	Axilla	Xiphoid	None		+	++	+++
I	12	6	—	6	0	0	12	2	1	0	0
II	27	14	7	6	4	2	21	8	3	1	0
III	22	13	2	7	9	1	12	12	4	1	2
IV	12	6	1	5	6	0	6	8	2	2	0
Total	73	39	10	24	19	3	51	30	10	4	2

and in seven cases at the xiphoid region. The murmur radiated in nine cases towards the axilla and once towards the xiphoid region. The murmur was not transmitted on 12 occasions. Out of the seven cases where regurgitation was found, the murmur was loudest in six cases at the apex and once at the xiphoid region; it radiated in six cases to the axilla. Twelve patients had mitral calcifications. It is interesting to note that of the seven patients with regurgitation, calcifications were present in six.

### 4. Systolic murmur of very loud intensity; Grade IV.

Of 12 patients (16%) who had a very loud apical systolic murmur, four had a mitral regurgitation at operation (two minimum and two

phoid region in 24. No radiation was noted in 51 cases. The murmur radiated 19 times to the axilla and three times to the xiphoid region. In 30 instances, calcifications were present at the time of operation.

In the 16 cases of mitral regurgitation (Table II) it is interesting to note that the maximum intensity was at the apex 14 times (87.5%) and at the xiphoid region twice (12.5%). The murmur radiated to the axilla nine times (56.2%). Calcifications were noted in 11 cases (63%).

We should add that, in this series of 150 operations for mitral stenosis, the surgeon found in three instances a slight insufficiency without a preoperative systolic murmur. One of these cases had calcification of the posterior leaflet.

When these three cases are added (Table II),

TABLE II.—MITRAL REGURGITATION WITH APICAL SYSTOLIC MURMUR

No.	Localization			Irradiation			Calcification	Regurgitation		
	Apex	Between	Xiphoid	Axilla	Xiphoid	None		+	++	+++
16	14	0	2	9	0	7	11	10	4	2
MITRAL REGURGITATION WITHOUT APICAL SYSTOLIC MURMUR										
3	Nil						1	3	0	0
Total	19	14	0	2	9	0	7	12	4	2

moderate). The murmur was loudest in six cases at the apex, once at the inner side of the apex, and in five cases at the xiphoid area. In six cases, the murmur radiated to the axilla, and in the other six it did not radiate at all. Calcifications were noted in eight instances.

Of the four cases of mitral regurgitation, three had calcifications. In three of these the murmur

the total number of cases of mitral regurgitation described by the surgeon amounted to 19, of which 12 had calcifications. This insufficiency was estimated to be minimal in 13 cases, moderate in four and considerable in two.

Subtracting the 16 cases of mitral regurgitation from the 73 having an apical systolic murmur, a group of 57 patients remains. In these, the sys-

toxic murmur was heard at its maximum at the apex 25 times (43.8%), at the inner part of the apex nine times (15.7%) and at the xiphoid process 23 times (40%). The murmur did not radiate in 44 cases (77.2%); in 10 instances it was transmitted to the axilla (17.5%) and in three cases to the xiphoid region (5.2%). Nineteen of these 57 patients (33%) had a mitral calcification. In this group of patients we frequently found the necessary elements for a diagnosis of organic or functional tricuspid insufficiency (Table III). This diagnosis was certain in 12 cases and probable in 15. Therefore, we

proved to be due to mitral regurgitation in 10.7% of cases and assumed to be due to tricuspid insufficiency in 18%. For the remaining 20%, we can give only hypothetical explanations (Table V).

#### DISCUSSION

This study concerns the first consecutive 150 patients operated on for mitral stenosis. It is understood that we have eliminated, as unsuitable for surgery, patients in whom we interpreted the apical systolic murmur as representing

TABLE III.—TRICUSPID REGURGITATION AND SYSTOLIC MURMUR

No.	Intensity of murmur				Apex	Localization		Calcifications	Regurgitation	
	I	II	III	IV		Between	Xiphoid		Certain	Probable
27	5	7	10	5	8	3	16	10	12	15

assume that in 27 instances the apical systolic murmur signified a regurgitation at the tricuspid orifice.

Elimination of these 27 patients leaves a group of 30 in whom we cannot find a satisfactory explanation for the etiology of the apical systolic murmur (Table IV).

TABLE IV.—SYSTOLIC MURMUR—ANY REGURGITATION

No.	Murmur intensity				Apex	Localization		Calcifications
	I	II	III	IV		Between	Xiphoid	
30	6	16	5	3	17	6	7	9

In summary, in our series of 150 proven cases of mitral stenosis, 77 (51.3%) had no apical systolic murmur. Only three of these patients (2%) were found to have a mitral regurgitation at the time of operation. The remaining 73 patients had an apical systolic murmur. It was

predominant mitral regurgitation. Therefore this study deals only with patients in whom the systolic murmur coincided with a surgically proven mitral stenosis corrected by digital, instrumental or combined commissurotomy.

In 19 cases the surgeon felt a mitral regurgitation: 16 of these patients had an apical systolic murmur and three did not. In the 16 cases where the systolic murmur signified regurgitation, the murmur was heard at its maximum at the apex in 14; it radiated in nine cases to the axilla, while mitral calcification was described in 11. With these facts, we feel able to predict a certain degree of mitral regurgitation when the following triad is observed: a systolic murmur maximal at the apex, its transmission to the axilla, and the presence of a mitral calcification. The greater the intensity of this systolic murmur, the more reliable this triad seems to be.

We feel that the degree of valvular rigidity, which reaches its maximum when the valve is calcified, plays a role in production of this systolic murmur. The incidence of calcifications in the total series of 150 patients is 31%. Actually, out of 77 patients without an apical systolic murmur, the percentage of calcifications is 22%, while in the 73 patients with a systolic murmur it is 41%. It is interesting to note that the incidence of calcifications rises to 68.7% in the group of patients having an apical systolic murmur and in whom mitral regurgitation was found (Table VI).

We are convinced that in a good number of cases an apical systolic murmur signifies a tricus-

TABLE V.—SUMMARY OF CASES WITH AND WITHOUT SYSTOLIC MURMUR

		No. of cases		Percentage
With syst. murmur	Mitral regurgitation . . . . .	16	10.7	28.7
	Tricuspid regurgitation . . . . .	27	18	
	No explanation . . . . .	30	20	
Without syst. murmur	No mitral regurgitation . . . . .	74	49.3	51.3
	Mitral regurgitation . . . . .	3	2	
	Totals . . . . .	150	100%	



TABLE VI.—INTENSITY OF SYSTOLIC MURMUR, MITRAL CALCIFICATIONS AND REGURGITATION

	<i>Systolic Murmur</i>			
	<i>Grade I</i>	<i>Grade II</i>	<i>Grade III</i>	<i>Grade IV</i>
Regurgitation...	8.3%	14.8%	31.8%	33.0%
Calcification....	16.6%	26.0%	54.0%	66.0%

pid regurgitation, either functional or organic. In this series, we have explained the systolic murmur on this basis in 37% of patients. A functional tricuspid insufficiency may exist in the same way as a functional mitral insufficiency. In the presence of a raised pulmonary pressure, it is to be expected that the right ventricle will enlarge. When this hypertrophy becomes considerable, it is logical to think that the tricuspid valve may become incompetent and permit a certain degree of regurgitation. This hypothesis has already been confirmed by electromanometric curves registered simultaneously in the right auricle and ventricle before and after commissurotomy. As regards organic tricuspid insufficiency, we have observed at postmortem many hearts with a tight mitral stenosis and also typical rheumatic lesions of the tricuspid valve. This leads us to feel that the association of mitral stenosis and tricuspid valvulitis is much more frequent than the literature indicates.

The clinical diagnosis of tricuspid insufficiency is easily made when the semeiological picture is typical. We believe that such a diagnosis should be suspected before the appearance of the classical signs. In the presence of mitral stenosis we suspect this condition when the systolic murmur is loudest in the xiphoid area or along the inner side of the apex. Its increase in intensity during post-inspiratory apnoea (sign of Rivero-Carvallo) is relatively common. Radiological and electrocardiographic evidence of right auricular and ventricular hypertrophy adds weight to this diagnosis. As already said, simultaneous registration of pressure in the right cavities of the heart has confirmed the diagnosis in many cases. With this background 27 systolic murmurs were explained in this series.

In only 16 cases of apical systolic murmur have we found the explanation by digital identification of mitral regurgitation at operation. In these cases, we have naturally interpreted the systolic murmur as reflecting this insufficiency. On the other hand, since in three cases of the total series there was mitral insufficiency with-

out a murmur, we must admit that the regurgitation per se may be clinically silent.

In 30 cases, this origin of the apical systolic murmur could not be objectively proven. It may be objected that digital palpation is not necessarily trustworthy and that it could give a wrong impression, especially when the regurgitation is minimal. We admit this possibility. However, it is by far the most precise criterion that we possess. It is better to accept the objective facts than to try to maintain theories built up in an epoch where they could not be substantiated objectively. We can readily state that in these 30 cases the systolic murmur did not signify a mitral regurgitation detectable by the finger. On the other hand, it was not associated with signs of a tricuspid lesion. It is very probable that it is associated with the mitral valvular lesion, but this hypothesis is far from proven. Analysis of the above facts makes it clear that an apical systolic murmur does not contraindicate a commissurotomy as long as it does not represent predominant mitral regurgitation. We feel able to eliminate this diagnosis by a careful study of the symptoms and of the apical systolic murmur, complete x-ray examination with fluoroscopy and routine electrocardiography. Much importance is given to x-ray and electrocardiographic signs of left ventricular hypertrophy; if these signs are found, surgery is ruled out. Catheterization of the right chambers of the heart is reserved for exceptional cases.

These criteria have proved reliable and therefore we do not attach too much importance, in a strictly clinical sense, to the different methods of exploring the left auricle: registration of pressure, evacuation time by angiocardiology, calculation of the mitral surface, electrokymography, etc. These methods, though not specific, seem to be superfluous in most cases.

#### SUMMARY

One hundred and fifty consecutive cases of tight mitral stenosis are reviewed. A systolic murmur heard at the apex or xiphoid area, or somewhere between, was present in 73 patients or 48.7% of the total group.

This murmur was thought to be due to mitral insufficiency in 16 cases, in which the surgeon felt a jet of regurgitation. In 27 cases the murmur was interpreted as due to tricuspid insufficiency on the basis of clinical, radiological, electrocardiographic and hæmodynamic findings.

In 30 cases, the authors were unable to explain the murmur with certainty. Deformities of mitral valve architecture (rigidity of the leaflets and chordæ tendineæ) and possible changes in the infundibular area are factors which may enter into the pathogenesis of the murmur.

As long as the systolic murmur does not indicate predominant mitral insufficiency, a commissurotomy can be performed. In the authors' opinion, differential diagnosis is possible by careful study of clinical symptoms and electrocardiographic and fluoroscopic signs, and occasionally by right heart catheterization.

In their total series of 258 consecutive patients operated upon, the percentage of error was only 1.16. On the basis of this acceptable margin of error, the authors do not feel justified from a clinical point of view in using systematically, in patients with an apical systolic murmur, the different objective methods described as permitting evaluation of the presence and significance of mitral regurgitation.

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#### RÉSUMÉ

Dans une série de 150 malades atteints de rétrécissement mitral serré, on perçut un souffle systolique chez 73, c'est-à-dire dans 48.7% des cas. Ces souffles étaient localisés soit à la région xiphoïde, soit à la pointe ou entre ces deux endroits. On les attribua à une insuffisance mitrale chez 16 d'entre eux (10.7%) lorsqu'à l'opération le chirurgien sentit au bout du doigt le jet de régurgitation. Cette méthode d'examen digital sans être parfaite n'en constitue pas moins le moyen le plus direct de vérifier la présence d'une insuffisance valvulaire. Cette sensation de jet fut aussi observée chez trois malades qui ne présentaient aucun souffle systolique. Dans 27 autres cas, ce souffle fut interprété comme un signe d'insuffisance tricuspiddienne d'après la confrontation des données cliniques, radiologiques, électrocardiographiques et hémodynamiques. On ne put trouver de raison satisfaisante pour expliquer le souffle des 30 autres malades. Parmi les facteurs qui contribuent à la pathogénèse des souffles se trouvent les déformations valvulaires, tels la rigidité des valvules, l'épaississement des cordages tendineux et les altérations possibles de l'infundibulum pulmonaire. La commissurotomie peut être pratiquée tant que le souffle systolique n'est pas le signe d'une insuffisance mitrale prédominante. Les auteurs de cet article croient pouvoir arriver à un diagnostic différentiel par une évaluation minutieuse des faits cliniques ainsi que des données des examens de routine (fluoroscopie, radiologie et électrocardiographie). Le cathétérisme ne devrait être réservé qu'aux cas exceptionnels. Ces mêmes auteurs n'attachent pas grand'importance aux méthodes d'exploration de l'oreillette gauche qui leur sembleraient souvent superflues. À l'appui de ces opinions, ils citent une série de 258 cas consécutifs qui subirent l'opération et où la limite d'erreur diagnostique fut de 1.16%.

#### LUDWIG'S ANGINA\*

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THE PURPOSE OF THIS PAPER is to emphasize certain dangers associated with the administration of anæsthesia for the surgical treatment of Ludwig's angina.

Ludwig's angina is now uncommon but it is still occasionally found. Patients who formerly would have developed Ludwig's angina as a result of dental disease, peritonsillar infection, or trauma to the floor of the mouth are today spared this serious complication by the early prophylactic use of antibiotics. However, there

always will be certain people who will develop this condition as a result of: (a) their ignorance of the value of antibiotics, (b) inaccessibility to antibiotics, or (c) improper employment of antibiotic therapy.

It is common knowledge that this disease formerly resulted in a very high mortality rate. In the pre-antibiotic days, 25 to 50% of these patients died because of asphyxia, septicæmia, bronchopneumonia or unknown cause.<sup>1,2</sup> Some deaths from unknown cause occurred during the anæsthetic phase and before any surgical intervention had been carried out. Numerous theories have been offered to explain these sudden deaths during attempts to produce anæsthesia, but none seems to apply universally. Some causes most commonly stressed are: (1) carotid body stimulation; (2) vagovagal reflex; (3) trauma to the larynx during the introduction of an intratracheal

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tube; and (4) laryngeal obstruction due to the infectious process.

To the inexperienced anaesthetist, the intratracheal tube would seem to be the answer to the problem of avoiding anaesthetic deaths in patients with Ludwig's angina. Actually, this may become an additional hazard—indeed a very dangerous hazard, since the laryngeal vestibule and perilaryngeal tissues are frequently oedematous because of lymphoid stasis consequent on circulatory interference.

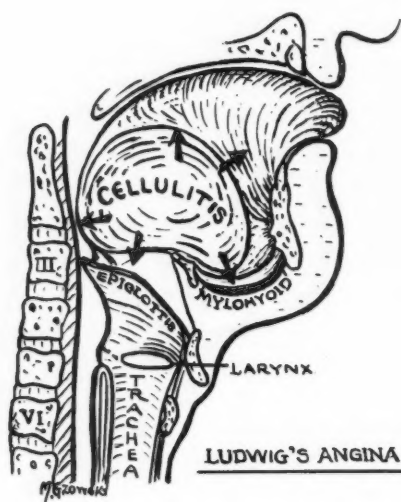


Fig. 1

Laryngeal oedema with the often accompanying trismus of the jaw prevents the insertion of the endotracheal tube into the larynx, and repeated unsuccessful attempts to do so may invite a fatal laryngospasm. It must be remembered that any interference with oxygen supply or elimination of carbon dioxide causes a chemical change in the blood. The oxygen lack, apart from its damaging effect on the brain, may also lead to increased oedema of the structures about the larynx.

The infectious process may also impinge on the laryngeal vestibule and glottis. The swollen, raised tongue, which is pushed upward and backward by the disease process, tends in time to force the already oedematous epiglottis further back, thus narrowing the airway to an even more dangerous degree (Fig. 1). In fact, the mere manipulation of the head during laryngoscopic attempts has been known to lead to sudden death in patients with deep neck infection.

Intravenous thiopentone (Pentothal) may appear to be an ideal anaesthetic agent for this

surgical condition, but it must be borne in mind that it frequently induces laryngospasm and bronchospasm whether or not curare or other relaxant is used; thus an additional hazard is presented to an already narrowed airway. However, after tracheotomy, there is no contraindication to the use of intravenous Pentothal.

When anoxia is present, the accessory muscles of respiration are called upon to help out with the respiratory exchange. Stimulation of the nasopharyngeal mucous membrane by irritant anaesthetic agents may cause reflex cessation of breathing or inhibition of respiration by paralysis of these accessory muscles. In the presence of toxæmia and an already overloaded or failing heart, the result may easily be death. As noted above, there are many opinions on the cause of sudden death in Ludwig's angina. Any one of many causes may predominate, but laryngeal obstruction should not be the cause of death merely because the danger is not recognized and appropriate measures are not taken to combat it.

Colby Hall<sup>3</sup> and Ashhurst<sup>4</sup> define Ludwig's angina as follows: "It is an acute inflammatory process involving the cellular tissues of the floor of the mouth and the submaxillary region of one or both sides of the neck. It is the simultaneous involvement of the submaxillary and sublingual tissues in a confluent septic cellulitis that warrants the condition being recognized as a distinct clinical entity." They further agree that the disease process may begin in either the sublingual or submaxillary area, but until it includes both it does not constitute Ludwig's angina.

Williams and Guralnick<sup>1</sup> emphasized that Ludwig's angina was commonly mistaken for other conditions in the floor of the mouth or in the area of the submaxillary gland. The disease is frequently diagnosed wrongly and confused with cervical adenitis, cellulitis of the submaxillary gland, or submental suppuration. They emphasize certain essential anatomical and clinical criteria in the diagnosis of Ludwig's angina. These bear re-emphasis.<sup>1</sup> "Anatomically there must be involvement of both the sublingual and submaxillary spaces. The former is recognized by oedema, induration, tenderness and elevation of the floor of the mouth, the mucosa of which is usually flecked with greyish-white exudate. The tongue may be so oedematous as to fill the oral cavity and protrude between the teeth (Fig. 2). Submaxillary space infection is

manifested by a rounded, tense, brawny, tender swelling which is greatest in the region of the submaxillary gland and limited to the suprahyoid region of the neck. Fluctuation is rare."

Clinically there is difficulty in speech, in swallowing, in opening the mouth and breathing. Difficulty in breathing usually indicates that the patient is critically ill. However, it must be kept in mind that the patient may die without having ever complained of difficulty in breathing. Cyanosis is not common; when it is present it is usually a premortem sign.

#### ETIOLOGY

In reviewing the case records of 24 patients\* treated for Ludwig's angina at the Montreal General Hospital, it was found that 11 cases occurred after dental extractions and one after an abscessed tooth. Two patients had widespread dental caries on admission. One case followed surgical exploration of Wharton's duct for calculi and occurred in spite of large prophylactic doses of penicillin (see Case 5). In nine the etiology was unknown.

Cultures from the mouth and from the abscess showed in almost every instance the usual oral flora. No specific organism could be identified as the cause. The ages of the patients ranged from nine years to 75 years.

#### TREATMENT

Early tracheotomy is the key to proper management of Ludwig's angina, and is the answer to avoiding deaths from acute laryngeal obstruction. We are aware of some cases of Ludwig's angina that have been cured by the use of antibiotics alone.<sup>5</sup> In many of these patients the abscess had spontaneously ruptured and drained through the floor of the mouth. It is not common for these infections to resolve completely without rupturing their bounds. At the present time, with more patients becoming sensitized to the antibiotics and bacteria becoming more resistant to them, the danger of waiting for spontaneous rupture of the infection, either into the floor of the mouth or elsewhere, is increased if surgical drainage is not employed early and in conjunction with the antibiotics.

In regard to surgical technique, it must be remembered that in Ludwig's angina the supra-

hyoid tissues of the neck are quite fused and the fascial planes are not easily identified. In contradistinction, the tissues in the infrahyoid region of the neck are easily distinguished. Therefore an elective tracheotomy should never be a technically difficult feat. It is our opinion that, once the tracheotomy has been done, general anaesthesia should be induced and maintained through the tracheotomy opening. Then incision and drainage of the fascial planes should be carried out.

When draining the infection, it is wise, after loosening the suprahyoid tissue planes, to place Penrose drains on each side of the midline within each of the deep fascial planes of the neck. One set of drains should be inserted deep to the anterior belly of the digastric muscles and the mylohyoid muscle, a second set of drains deep to the geniohyoid muscles, and a third set deep to the genioglossus muscles in close relation to the periosteum of the mandible and the mucosa of the mouth. Antibiotic culture studies are done and when feasible a specific therapy is started.

Thus, the combination of (a) early tracheotomy with local anaesthesia, (b) complete drainage with release of tension of the fascial planes under general anaesthesia,<sup>6</sup> and (c) employment of antibiotics would seem to be the safest and best method of treating Ludwig's angina.

#### CASE HISTORIES

The following case histories and comments illustrate various significant points in the treatment of this condition.

##### CASE 1

P.B., aged 58 years. Admitted September 27, 1940. Died September 29, 1940. Diagnosis: Ludwig's angina: Two weeks before admission, a sudden swelling of the front of the neck developed and gradually increased in size. Two days before entry, he began to have difficulty in breathing. A diagnosis of diphtheria was made and he was sent to the Alexandra Hospital, then to the Montreal General Hospital. On admission, he was in great respiratory difficulty. The neck was so swollen that the chin and the chest were continuous. The swelling was hot, red and tender. On the day of admission the patient was taken to the operating room and under 1% procaine local infiltration, a tracheotomy was done. Then under i.v. Evipal, incision and drainage was performed. He was put on sulfonamides and given a blood transfusion. He died at 4.30 a.m., September 29, 1940.

*Postmortem.*—Ludwig's angina; acute ulcerative tracheitis; bilateral bronchopneumonia; arteriosclerotic kidney.

\*Two of the above cases presented in the last three months.



*Comment.*—This case demonstrates that there is a surgical "point of no return". There was too long a delay (two weeks) before adequate surgery and chemotherapy was provided. Penicillin and the more modern (and more useful) antibiotics were then unavailable.

#### CASE 2

J.L., aged 21 years. Admitted May 22, 1952. Discharged June 28, 1952. Diagnosis: Ludwig's angina: Five days previously, swelling of the left side of the neck. Two days previously, rapid increase in swelling. History of toothache, but no dental interference. On admission, there was stridor, marked swelling of the left suprahyoid region, marked trismus, bulging of left pharyngeal wall in the region of the soft palate, and dental caries and gingivitis. The swelling of the floor of the mouth and of the neck was brawny.

He was admitted to the Montreal General Hospital and taken to the operating room about three hours later. Before any interference, the abscess opened into the mouth spontaneously and some pus drained out. He was returned to the ward and put on antibiotics. The following day, stridor persisted and a tracheotomy was done under local anaesthesia. General anaesthesia was induced through the opening, and incision and drainage of the infected area was carried out. The patient made a complete recovery.

*Comment.*—This case illustrates the important point that usually nothing is gained if we delay the tracheotomy in the hope that the antibiotics and spontaneous drainage alone may cure the patient. In this instance, the tracheotomy had to be done as well as the incision and drainage, after endangering the patient's life needlessly.

#### CASE 3

T.I., aged 48 years. Admitted October 3, 1952, at 12.00 noon, with a one-week history of swelling of the floor of the mouth, apparently secondary to a dental infection in one of the left lower canine or first premolar teeth. For four days before admission, the swelling had increased markedly in size, and the patient had been unable to swallow for a day before admission.

The head was extended on the neck, and a hard brawny swelling occupied the anterior neck inferior to the mandible; this was only slightly tender to palpation. There was moderate respiratory difficulty and trismus. A red, hyperaemic swelling in the buccal floor forced the tongue almost to the roof of the mouth. The posterior pharyngeal wall could not be visualized.

Temperature on admission 101.6° F., pulse 80, respirations 20 and white cell count 12,500. The patient was started on large doses of combined penicillin and streptomycin therapy (Fortimycin) and 2000 c.c. of i.v. fluids. By 6.30 p.m. on the day of admission, he became restless and experienced some difficulty in breathing; oxygen was started by nasal catheter, with apparent relief. By 10.30 p.m., the pa-

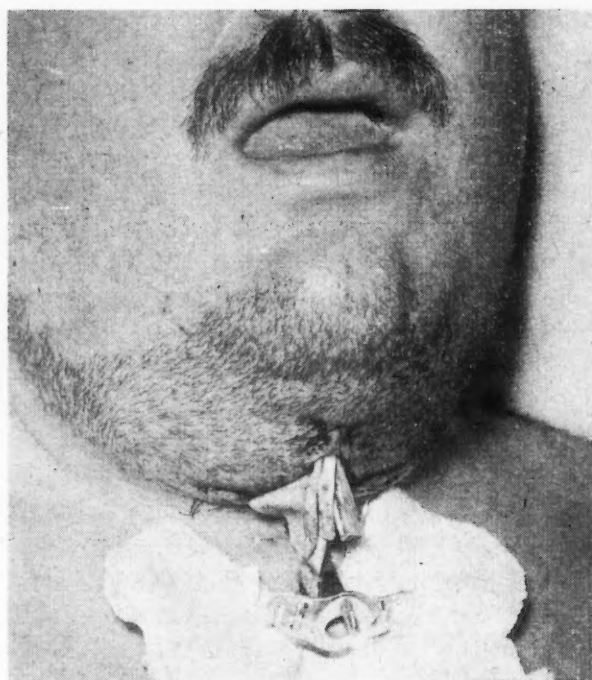


Fig. 2

tient again experienced difficulty in breathing, and a tracheotomy was performed. Profuse amounts of thick mucoid secretions were aspirated from the tracheobronchial tree. The patient began to swallow three days after admission. Fortimycin was discontinued on November 17, after the patient had

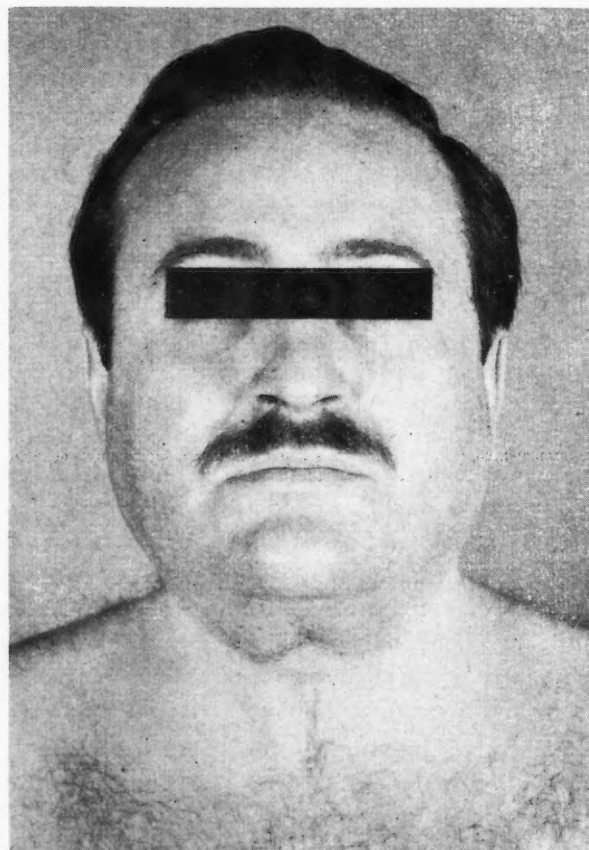


Fig. 3



received a total of 21,600,000 units of penicillin and 72 g. of streptomycin. Cultures from the area were reported to show "usual respiratory flora".

*Comment.*—Here again, tracheotomy was delayed for an unnecessarily long time and finally had to be performed anyway, since the antibiotics alone proved insufficient to cure the patient.

#### CASE 4

S.S., aged 38 years. Admitted June 20. Discharged June 30, 1945. Diagnosis: Ludwig's angina: Two days before admission, sore throat followed by swelling in the floor of the mouth and fever. On admission, the tongue was pushed up against the roof of the mouth. There was a large, hard swelling in the front of the neck. On the day of admission, a tracheotomy was done under local anaesthesia. Through the tracheotomy opening, cyclopropane and oxygen were given for incision and drainage of the swollen area. A small amount of pus was obtained from the floor of the mouth on the left side. Discharged June 30 to return July 6 for closure of the tracheotomy wound. The patient returned on that date and the wound was found to have closed spontaneously.

*Comment.*—This demonstrates that, when basic principles are employed in proper sequence, i.e., early tracheotomy, proper anaesthesia and surgical drainage, cures are obtainable even though antibiotics are not employed. It also emphasizes that most tracheotomies heal without further surgery.

#### CASE 5

Dr. J.G., aged 32 years. Admitted March 3, 1956. Discharged March 14, 1956. Diagnosis: Ludwig's angina: Recurrent attacks of left submandibular gland infection due to calculi in Wharton's duct. Attempted surgical removal of calculi at another hospital on March 2, 1956, via an oral incision, led to the development of Ludwig's angina in spite of large doses of prophylactic penicillin. On admission, temperature was 100.6° F. The patient was toxic, dehydrated and dyspnoeic. There was no stridor but he could not swallow his saliva. His speech was garbled. The tongue was very swollen and pushed up to the roof of the mouth (Fig. 2). It was prolapsed through the front teeth. Fig. 2 is a photograph taken 36 hours after emergency operation and shows the prolapse of the tongue, which was still present but to a lesser extent than on admission. The neck was swollen bilaterally.

*Treatment.*—Tracheotomy under local anaesthesia (A.A.G.) was performed, followed by intratracheal general anaesthesia and incision and drainage of the suprahyoid space by undermining the fascial planes as previously described. This was performed without incident. Six Penrose drains were inserted (Fig. 2). The left mylohyoid muscle was cut across transversely to release tension. The patient made an uneventful recovery, with minimal scar tissue deformity of the neck (Fig. 3). The left submaxillary gland then returned to normal.

#### SUMMARY

Where suppuration involving the pharynx and larynx occurs, the importance of providing an adequate airway by tracheotomy cannot be too strongly stressed.

Where operation is contemplated, general anaesthesia should not be attempted until a tracheotomy has been performed.

An early tracheotomy followed by surgical drainage of the abscess and adequate antibiotic therapy is the treatment of choice.

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#### RÉSUMÉ

L'anesthésie dans l'angine de Ludwig présente des dangers importants. Avant que n'apparaissent les antibiotiques, cette affection entraînait une forte mortalité de l'ordre de 25 à 50%. Sa fréquence de nos jours est heureusement diminuée. L'intubation endotrachéale difficile dans ces cas, loin de résoudre le problème, peut au contraire rendre la situation plus périlleuse en provoquant un laryngospasme. On a déjà rapporté qu'une simple manipulation de la tête dans cet état peut amener une mort subite. Le thiopental ne doit être employé qu'après trachéotomie puisqu'il risque de déclencher lui aussi un spasme du larynx. Pour qu'il existe réellement angine de Ludwig, il est essentiel que soit pris dans le processus inflammatoire les espaces sous-lingal et sous-maxillaire. La langue peut être si œdématiée que la bouche ne suffit plus à la contenir. Le gonflement de l'espace sous-maxillaire s'étend jusqu'à la région sous-hyoidienne. Le trismus, la dysphagie, et la dyspnée complètent le tableau clinique. La cyanose lorsqu'elle s'y trouve comporte un pronostic funeste. La majorité des 24 cas vus à l'Hôpital Général de Montréal survint à la suite d'un état septique des dents. Le traitement est basé sur le drainage par incision secondé par l'emploi d'antibiotiques. Cinq cas sont cités en exemple.

#### RIGHT HEPATIC LOBECTOMY

Occasionally a single large secondary deposit in the right lobe of the liver is apparently the only metastasis of an operable primary cancer in the gastro-intestinal tract, and a formal removal of the right half of the liver seems a logical procedure. Anatomical studies in the postmortem room were made by Lloyd-Davies and Angell (*Brit. J. Surg.*, 45: 114, 1957) to devise a method of right hepatic lobectomy that would not entail gross blood loss, and would allow a safe retreat if insuperable difficulties were encountered. This depends on a determination of the individual variation in the termination of the hepatic veins. Successful ligation of the right hepatic and of any other important vein from the right lobe can be performed, when the anatomy is clear, through an abdomino-thoracic diaphragm-splitting exposure. The operative technique is described as carried out in a patient who is alive and apparently free from recurrence 2½ years later.

## ASSESSMENT OF DRUG TOXICITY IN CANADA

REGULATIONS for the sale of new drugs in Canada went into effect in September 1951. Since that time, drug manufacturers have been required to submit to the Food and Drug Directorate pertinent information to show that their products are safe for the uses recommended.

It is common knowledge that a new drug should be studied first in the laboratory and then in the clinic; the details of the study will depend on the nature of the ingredients and the intended uses. For most new drugs, a general plan of study can be followed which will permit an understanding of the usefulness and toxic properties of the drug.

In the four papers which follow some of the principles and procedures which have been helpful in making an appraisal of the toxicity of new drugs are outlined.\*

### 1. Acute, Subacute and Chronic Toxicity Tests in Animals

M. G. ALLMARK

In the evaluation of the safety of a new drug the acute toxicity is usually determined first. It should be determined on at least two species of animals by oral and parenteral administration. The rat or mouse is used for one species and a non-rodent for the second species. It is often advantageous to determine the acute toxicity on three or four species. A sufficient number of animals are used on several dosage levels so that it will be possible to determine the  $LD_{50}$ . It is also desirable to compute the slope of the dosage-mortality curve and its variance; these along with the  $LD_{50}$  will define the acute toxicity of a drug more precisely and enable a comparison to be made with other drugs of similar properties.

For drugs to be administered by inhalation or applied over the skin or the mucous membrane, the acute toxicity should also be determined in animals by these routes of administration.

There are many factors which influence absorption and thus, indirectly the toxicity. These are: (1) the physical state of the drug—for example, dry chemicals are more slowly absorbed than those administered in solution; (2) solvents—for example, substances dissolved

in oil are absorbed more slowly than those in water; (3) concentration of the drug—for example, concentrated solutions are usually more rapidly absorbed than the same amount in a more dilute form; (4) presence of other substances—for example, suspending agents may hinder absorption of the drug. In reporting the results of acute toxicity tests, all these details should be stated. It is essential, also, to note the nature, time of onset, severity and duration of all toxic signs or symptoms. The animals should be observed for at least two weeks. This observation period may be extended if the animals appear sickly.

The animals that die and those that survive these acute toxicity tests should be autopsied. A gross examination of the organs is usually all that is done in these experiments. In some cases if the cause of death is not apparent, some of the more important organs should be examined histopathologically. It is also well to check the blood for haemoglobin and for red, white and differential cell counts.

Subacute toxicity studies are usually carried on for six to 12 weeks and chronic studies up to a year or longer, depending on the type of product under investigation. In this type of experiment, it is usual to feed or inject daily graded doses of the drug to groups of one or two species of animals, preferably rats and one other species such as the dog or monkey. During the testing period, observations on each animal should include rate of growth, food intake and general appearance and behaviour. A complete haematological examination and certain organ function tests should be done on a few of the animals on each dosage level. At the end of the experiment the animals are sacrificed and gross and microscopic pathological changes are observed. In the chronic toxicity studies it is advisable to sacrifice one or two rats of each sex in each group at six months or other suitable intervals, for pathological examination. Generally this type of test should define the long-term toxicity of a drug, and provide a reasonable estimate of the lowest dosage required to produce gross and microscopic changes.

Many other tests can be applied to these animals, but their selection usually is based on gross symptoms, functional changes, and pathological changes observed during the course of the experiment.

\*These articles are based on papers presented at the Annual Meeting of the Pharmacological Society of Canada, held in Montreal on October 17, 1956. The first three authors are members of the staff of the Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Canada. Dr. J. R. MacDougal is a member of the staff of Frank W. Horner Ltd., Montreal, Que.



## 2. Pertinent Pharmacological Studies in Animals

F. C. LU

In addition to the routine acute and chronic toxicity tests, many pharmacological studies are usually carried out on a new drug to demonstrate its therapeutic action as well as its various toxic effects. The demonstration of the therapeutic action of a drug is fundamental to the estimation of the therapeutic index and to the determination of the mode of action; the significance of these will be discussed elsewhere in this paper.

Many satisfactory pharmacological procedures are available for the demonstration of various therapeutic actions of most drugs. These procedures may be readily found in the literature and thus require no detailed discussion here. However, it may be noted that the species of animals used is sometimes a matter of considerable importance. For instance, the emetic property of a drug is usually studied in cats and dogs, and rodents are totally unsuitable. Furthermore, in order to demonstrate certain therapeutic actions, animals with pathological changes may have to be used. For example, hypertensive animals are sometimes preferable to normotensive ones in ascertaining hypotensive action. Similarly, hypodynamic hearts, vitamin-deficient animals, etc., are useful in demonstrating certain specific effects. It may also be noted that the use of antagonists or synergists is sometimes valuable in defining the action of a drug.

Following the demonstration of the therapeutic action, the mechanism and site of action of the drug are then studied. Some knowledge about the mechanism and site of action of a drug is conducive to safety, because when the pharmacological nature of a drug is well known, the drug may be used clinically in a more rational manner. Moreover, useful synergists to the drug may be instituted and harmful combinations of drugs may be avoided. Finally, pharmacological antidotes may be developed for cases of poisoning resulting from overdosage of the drug or hypersensitivity of the patient.

In assessing the safety of a new drug, a thorough understanding of all toxic effects is also essential. Some of the toxic effects of a drug may be elicited in animals even when doses that produce the therapeutic action are given; others are demonstrable only after larger doses. Animals given the higher dosages of a drug

may be considered as corresponding to hypersensitive patients following the administration of a therapeutic dose. Thus, by increasing the dose of a drug the toxic effects that occur occasionally may be produced more or less regularly.

In the following list are some of the readily observable changes in the various systems which may be associated with the administration of a drug:

1. Central nervous system and skeletal muscle: excitation, sedation, ataxia, tremor, convulsions and abnormal posture.

2. Autonomic nervous system: laceration, salivation and dilatation or constriction of pupils.

3. Cardiovascular system: changes in heart beat and blood pressure, and cardiac arrhythmias.

4. Respiratory system: depression or stimulation of respiratory movement in its rate or volume, irregular rhythm and excessive secretion in the respiratory tract.

5. Gastro-intestinal tract: retching, vomiting, diarrhoea and constipation.

Dogs are the preferred species of animal for these studies. It may be noted that while these changes may also be observed in the acute and chronic toxicity tests as outlined in the preceding paper, more exact and objective methods are usually adopted in these pharmacological investigations.

Results obtained in these preliminary investigations are usually helpful in deciding the type of additional pharmacological experiments to be carried out. The chemical nature and therapeutic actions of a drug may also guide the selection of further special studies. For example, chemicals containing chlorine should be investigated for possible cardiac and hepatic toxicity, and addiction liability should be determined for all analgesics.

After a drug has been thoroughly investigated as to its various toxic effects, the doses that produce these effects should be estimated. The minimal dose that induces any major toxic effect and the dose that elicits the therapeutic action should then be determined accurately in at least two species of animals. The ratio of these two doses is the therapeutic index; as a rule, the greater the index, the safer the drug. In these quantitative studies and others where comparative evaluations are involved, the adoption of a proper experimental design and the

use of an adequate number of animals or test objects are essential in minimizing bias and in reducing the variance. The data obtained should be subjected to a suitable statistical analysis in order to estimate the activity or toxicity and to determine the variance of the estimate. It should also be noted that if the variation between the responses of different species of animals to a drug is large, the animal data should be interpreted with great caution.

The extent of the pharmacological studies required is in general dependent upon the following factors: (1) The duration of administration. Drugs to be used for a long period of time should be studied more thoroughly than those to be used for a short period. (2) The severity of the conditions for which the drug is to be used. For example, more extensive investigations of the untoward effects should be carried out for drugs to be used in minor diseases of long duration than for drugs to be used in acute fatal diseases. (3) The therapeutic index. Generally speaking, the smaller the index the more extensive the studies should be.

### 3. Biochemical and Miscellaneous Studies

W. DONALD GRAHAM

The following is a summary of some of the biochemical and other studies required. It is to be emphasized that additional special investigations of varied nature may be required in specific instances.

The presence of contaminants, their nature, and their amount should be known. It is important to know the extent of variations in purity from lot to lot. Information on the solubility of the drug in various laboratory solvents and in body fluids may assist materially in furthering knowledge of the behaviour of the drug. Methods for the determination of the drug in pure form and in the forms in which it may occur in body tissues or fluids should be provided. Any possible interference with clinical laboratory methods should be noted.

Studies should be made to assess possible irritation of tissues with which the drug may come in contact during administration and absorption. If the drug is given orally, it is desirable to know the site of absorption and whether the drug is stable in gastric fluids. The method by which the absorbed drug is transported and the location in which it is stored are very useful information. The route of excretion and whether

the drug is degraded, conjugated, etc., or unchanged before it is excreted are important. It is desirable to know whether the drug is completely excreted. A drug given frequently and in considerable amount should be examined for possible carcinogenicity, particularly if it is retained in the body for long periods or is chemically related to known carcinogens. Possible damage to kidney or liver should be assessed by the use of suitable function tests. Special tests may be indicated in particular cases. If the drug causes anaemia or other dyscrasia, its effect on haemoglobin levels, on blood-forming organs, on the white cells, or on the clotting system should be checked. If possible, the mechanism of such effects should be elucidated.

The mechanisms by which the drug exerts its beneficial and toxic effects should be determined if possible. The drug may act by inhibiting some important enzyme system (for example, the effect of prostigmine on cholinesterase). If this be ascertained, an extensive study of the particular system involved is indicated. Information of this type might enable detection of very early signs of toxicity. If the drug itself is an enzyme, its effect on various tissues under conditions of use should be evaluated.

It is advisable to check routinely for antigenicity and for the presence of histamine-like activity in products derived from animals or micro-organisms. Tests for sterility and pyrogenicity should be carried out for all parenteral products. Certain other drugs must also be sterile.

### 4. Clinical Pharmacological Studies

J. R. MacDOUGAL, M.D.

The purpose of clinical data in the new drug submission is to demonstrate that no undue toxic reactions have been encountered during the clinical trial of the drug and that the medicament is safe for the use recommended. It also provides an opportunity to suggest precautions that should be brought to the physician's attention.

In order to obtain the clinical data on a new drug, a clinical trial is carried out. There are various grades of clinical trials ranging from the collection of clinical testimonials to the performance of clinical pharmacological studies. Statements based on clinical testimonials are



often difficult if not impossible to evaluate. Clinical pharmacology, on the other hand, is a means whereby drugs may be examined in a scientific manner, reducing the effects of chance and psychological influence as much as is humanly possible. It involves the use of proper controls, suitable criteria for evaluating the effects of the drug, and statistical analysis of the data.

In carrying out clinical trials the investigator should evaluate not only the efficacy of the drug but also its toxicity. While the toxic reactions observed in animal studies should receive special attention during a clinical trial for their possible occurrence in human subjects, other untoward effects which are not readily demonstrable in animals should be investigated also. One of these is blood dyscrasia. It is therefore important in clinical investigation to have a series of detailed blood examinations even when the drug has not been found to affect the blood picture in animals. It is also desirable to present records showing the results of urinalysis, organ function tests and other laboratory examinations that were performed before, during and after the treatment. In addition a clinical investigator should attempt to determine the nature of the reaction, if a reaction occurs, and to evaluate its significance.

Glowing and enthusiastic reports on new drugs sometimes appear in lay publications before authoritative information is published in the medical literature. This premature publicity often results in a demand for the drug by the public before the drug has been thoroughly studied by the clinical investigator. Experienced physicians know that the therapeutic usefulness of a new drug is sometimes exaggerated, and considerable modification of the early reports may have to be made.

The usual claim made for a new drug is either that it is more active or that it is less toxic or produces fewer untoward reactions than similar preparations. This may be true. On the other hand, if these claims are made on the basis of clinical trials with a small number of patients, their validity may be questionable. In order to justify the claims made for a drug, there is no substitute for prolonged, controlled clinical evaluation on a large number of patients. The number of patients that should be included in a clinical investigation is dependent upon many factors such as the disease state involved,

availability of patients, and the time element.

It may also be noted that the advertising of a drug must correspond to the facts disclosed by the experimental data. Directions for use which are shown on the label or listed in the package insert should be adequate for the proper use of the drug. Precautionary measures to be taken must be clear and concise. Contraindications should be listed, and it is desirable to outline therapeutic measures to counteract the toxic effects of the drug.

While clinical data assembled in Canada can be, and often are, checked by representatives of this department, those assembled in the United States can also be investigated if necessary. On the other hand, data on new drugs assembled outside of this continent cannot be verified readily. For these new drugs it is therefore desirable to carry out some clinical work in Canada to confirm the foreign data. It may be noted also that many drugs are in clinical trials in foreign countries before adequate animal experimentation has been conducted. In such cases the clinical investigation carried out in Canada when animal data are available will serve to supplement the foreign work.

It is realized that there are certain factors which will limit the adequate clinical evaluation of drugs in Canada. One of these factors is the small number of patients usually available for clinical trials. Another factor is the small number of physicians interested in doing this type of work. These problems are, however, not insurmountable and might be overcome by the establishment of effective medical departments in the various companies and by closer co-operation with the medical schools as well as the numerous hospitals and clinics throughout the country not directly associated with the medical schools.

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#### CONTACT DERMATITIS DUE TO CREASELESS FABRICS

Andrup, an Oslo dermatologist, reports that among one hundred consecutive patients suffering from contact dermatitis, 24 gave a positive patch test to formaldehyde (*Tidsskr. norske Lægefor.*, 77: 679, 1957). Of these 24 persons, four women and one man had a marked eczematous reaction to creaseless fabrics, made creaseless by finishing with a condensation product of urea and formaldehyde. It is thought that the fabric may give off small quantities of formaldehyde and thus cause contact dermatitis in sensitive persons.

## SEROLOGICAL REACTIONS TO POLYSACCHARIDES IN RHEUMATOID ARTHRITIS\*

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SEROLOGICAL PECULIARITIES in rheumatoid arthritis have been intensively studied in recent years. Most investigators have used agglutination reactions to demonstrate the presence in serum from patients with rheumatoid arthritis ("rheumatoid serum") of a reactant which is relatively specific for the disease. The nature of this factor, or factors, is still undetermined, although the best evidence at present indicates that it is a gamma globulin. This work is well documented and has been the subject of competent reviews in recent publications.<sup>1, 2</sup>

One of the first test systems to be widely studied demonstrated the ability of rheumatoid serum to enhance, to an unusual degree, the agglutination of antigenic particles (e.g., sheep red cells) sensitized with subagglutinating quantities of specific antibody. With few exceptions, sera from normal subjects or from patients with other diseases did not exhibit this property. It was then shown by Heller<sup>3</sup> that some normal sera would inhibit this enhancement and that this inhibition was contained in the Fraction II (Cohn) of the serum. Heller concluded that this phenomenon was due to competitive inhibition. He subsequently sensitized tannic acid treated red cells with Cohn Fraction II of pooled human serum and the resulting "F II test" showed the same relative specificity for sera from patients with rheumatoid disease as did the enhancement procedures. It was therefore postulated that in the F II test a combination was taking place between a reactant in rheumatoid serum (called the R factor) and some component of the F II globulin coating the treated red cells, the subsequent agglutination of the red cells serving as a visible indication of the underlying

ing reaction. The nature of this reaction is still undetermined. It has been postulated that it is an antigen-antibody combination, although some features are not in accord with characteristics of known antigen-antibody reactions. So far it has not been possible to isolate and define precisely either the R factor or the active component of the Cohn Fraction II. With regard to the latter it is of interest that some preparations of this fraction are inert but can be made reactive by exposure to heat or to acid.<sup>1</sup>

A recent modification of the F II test uses polystyrene globules in place of the tannic acid treated red cells.<sup>4, 5</sup> These particles are suspended in a solution of Fraction II of pooled human serum in sodium borate buffer at pH 8.2. After this procedure, which is presumed to coat the latex particle with some component of the Fraction II, the particles are added to serial dilutions of test serum and incubated; agglutination of the particles is read as a positive reaction. This latex fixation test (herein called the F II latex test) has a specificity for rheumatoid serum comparable to that of earlier tests. The original work of Singer and Plotz on this test system has been confirmed recently.<sup>6</sup>

This report is concerned with the demonstration of three test systems employing the method and components of the F II latex test\* but using chondroitin sulfate, hyaluronic acid and heparin, respectively, as sensitizing agents in place of the Cohn Fraction II of pooled human serum.

### METHOD

Five concurrent tests were conducted on each serum specimen. All blood specimens were drawn in ordinary sterile syringes, allowed to clot and the serum removed. Tests on all sera were set up within four hours of collection.

The five tests are:

1. F II latex test—by the method of Singer and Plotz using borate buffer at pH 8.2.
2. F II latex test procedure omitting the F II globulin ("latex only" test) in borate buffer at pH 8.2.
- 3, 4, 5. F II latex procedure substituting for the F II globulin in test 3, 4, 5, respectively, a 1% solution of chondroitin sulfate,† a 1% solution of hyaluronic acid‡ and a solution of heparin‡ containing 1000 international units/c.c. (approximate—

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\*Latex particles kindly donated by Dow Chemical Co., Midland, Michigan.

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ly 11 mg./c.c.). These tests are run in borate buffer at a pH of 7.9.

Chondroitin sulfate and hyaluronic acid are obtained commercially and are derived from bovine sources. Heparin is a standard commercial preparation. A small series of tests used chondroitin sulfate from human autopsy material\* (prepared by the method of Einbinder and Schubert<sup>7</sup>) and identical results were obtained. Results in this report refer only to bovine chondroitin sulfate.

cimen collected usually after an interval of several weeks. This series of repeated tests in fresh sera allowed some assessment of the reproducibility of a test on a given patient, although the quadrupling dilutions did not allow accurate establishment of an end point. It will be noted that variability was not infrequent. Numerous repeated fresh specimens taken from chronic disease controls and normal subjects were tested and no significant variability of test results was demonstrated.

TABLE I.

Patients	F II Latex			Latex only			Chondroitin latex			Heparin latex			Hyaluronic latex		
	Pos.	NR*	Neg.	Pos.	NR	Neg.	Pos.	NR	Neg.	Pos.	NR	Neg.	Pos.	NR	Neg.
71 Rheumatoid arthritis.....	59	4	8	14	25	32	50	16	5	51	13	7	47	5	2†
	83%	6%	11%	20%	35%	45%	70%	23%	7%	72%	18%	10%	87%	9%	4%
75 Normal.....	2	73		4	71		5	70		4	71		5	53†	
	3%	97%		5%	95%		7%	93%		5%	95%		9%	91%	
84 Chronic disease.....	7	77		1	83		10	74		6	78		8	47†	
	8%	92%		2%	98%		12%	88%		7%	93%		15%	85%	
48 Lymphomas‡.....	5	43		0	48		4	44		5	43		1	36†	
	10%	90%					8%	92%		10%	90%		3%	97%	
7 Ankylosing spondylitis...	1	6		0	7		1	6		1	6		0	6	
14 Osteoarthritis.....	0	14		0	14		0	14		1	13		0	12	
5 Gout.....	0	5		0	5		1	4		0	5		1	4	
2 Lupus erythematosus.....	1	1		0	2		1	1		1	1				
4 Polyarteritis nodosa.....	1	3		0	4		2	2		1	3				
2 Dermatomyositis.....	0	2		0	2		0	2		0	2		1	1	

\*"NR" means non-reproducible, i.e., in two or more tests run on different fresh sera from the same patient (drawn with an interval of days or weeks) positive on some occasions and negative on others (see discussion of results).

†Note that hyaluronic latex tests were done on a smaller series.

‡Sera from this group of chronic diseases happened to be available to us.

Patients were categorized according to the criteria of the American Rheumatoid Foundation.<sup>8</sup> The group designated as R.A. includes only those defined as "definite rheumatoid arthritis" by these criteria. Results on patients in the "probable" or "possible" category are not included in this paper.

Sera for testing were set up in quadrupling dilutions from 1/5 to 1/5120 to allow a survey over a wide range. Tests were read as positive if agglutination appeared in any of the three tubes containing dilutions 1/20, 1/80, 1/320. A positive reaction in the 1/5 dilution in normals was not uncommon in the chondroitin latex test and less common in the other two polysaccharide tests; most rheumatoid sera gave a positive reaction in these tests to 1/80 or beyond. The criterion for a positive test was selected as that showing the most consistent difference between rheumatoid disease and controls.

Agglutination in the polysaccharide tests is definite and easily read at pH 7.9. When run at pH 8.2 (as in the F II latex test) these polysaccharides tend to "cake" in the bottom of the tube.

All patients with rheumatoid arthritis had two or more separate specimens tested, the second spe-

## RESULTS

The results of the five tests run in parallel are shown in Table I.

The results on rheumatoid sera show several interesting features:

1. The percentage of positive results in the F II latex test is somewhat higher than previously reported.<sup>5,6</sup> This is probably related to the relatively strict criteria used to select this group of patients; all had clinically well-defined disease and in most it was relatively widespread and of considerable duration.

2. Eight sera were negative in the F II latex test, seven from females and one from a male. These sera showed different results in the polysaccharide tests. The specimen from the male was consistently negative in F II latex, but positive in both chondroitin sulfate and hyaluronic acid and variably positive/negative in heparin. Of the seven specimens from females none was consistently negative in all polysaccharide tests; five were variably positive/negative in one or more polysaccharide tests and three were con-

\*Kindly supplied by Dr. H. E. Taylor, Professor of Pathology, Faculty of Medicine, University of British Columbia.

sistently positive in one or more polysaccharide tests. Thus, no specimen of the 71 rheumatoid sera was consistently negative in all test systems.

3. Four sera from patients (6%) with rheumatoid arthritis, when tested by the F II latex procedure, gave inconsistent results in separate fresh specimens of sera. It is known that this test does not show a good reproducible end point<sup>4</sup> and variation in titre is not uncommon in our experience. In the four patients mentioned the variation in titre from one fresh specimen to another was marked and usually involved a change from a strongly positive test (1/5120) to a definite negative in all dilutions. Three of these patients have been tested numerous times in the past two years by the F II latex procedure and by the sheep cell agglutination test of Rose. They have shown this same marked variability of titre in both tests and without apparent relation to activity of the rheumatoid disease. The fourth patient was a 23-year-old woman with rheumatoid arthritis of four years' duration, with widespread disease of a low-grade intermittent activity and without gross joint destruction. She had negative polysaccharide and F II tests while enjoying a definite remission during pregnancy and positive tests appeared two months postpartum associated with a clinical exacerbation.

Variability of titre in the polysaccharide tests is common, often amounting to a two-tube (quadrupling dilutions) difference from one serum sample to another. Variability sufficient to modify a result from positive to negative is more frequent in these tests than in the F II latex procedure. It may be related to the lower titre found in all the polysaccharide tests as contrasted to the very high titres in the F II latex test.

4. A relatively high percentage of rheumatoid sera (20%) showed a positive or variably positive (35%) reaction when latex particles alone (latex only) were added. When agglutination was produced in this fashion, it usually occurred over a wide range of dilutions, so that the reaction must be considered as quite definite. An incidence of 11% of positive reactions in the latex only test has been reported previously.<sup>5</sup> In our hands this reaction to latex only is quite variable from one specimen to another. We noted that the F II latex test of two different sera from the same patient might be consistently strongly positive whereas the latex only reaction on the

same specimens might be negative in one and positive in the other. We believe that variation in technique can be excluded, as there was no tendency for the latex only positive reactions to be more frequent on one day than another.

However, there was a strong tendency for high-titre positive results in the F II latex to be associated with the positive latex only test. The titre in the F II latex test may vary somewhat from specimen to specimen in the same patient and it was possible to note a frequent association between low-titre F II latex sera and reversion of the latex only reaction to negative. In addition to this, all consistently negative F II latex sera were also consistently negative in the latex only reaction. This suggests that the presence of a positive reaction in the latex only test is associated with a quantitative increase in rheumatoid factor. However, the association with the F II latex titre is not absolute and this explanation may not be adequate.

All tests (except latex only) showed a larger number of "false" positives among chronic disease controls than has been previously reported by others.<sup>1, 5, 6</sup> It is difficult to compare the findings of different investigators, as types of chronic disease are not specified. It is noteworthy in our series that most of these positive reactions in chronic disease controls occurred in the same patients throughout all tests. For instance, a chronic alcoholic, two patients with cancer, one with Hodgkin's disease and one with a chronic empyema of 15 years' duration gave positive results in at least three out of four tests. The peculiarity of these sera would seem to be in some way similar to that found in rheumatoid arthritis. All of these positive reactions, however, appeared only in low dilutions, in no case beyond 1/80.

The percentage of positive tests in normal controls was slightly higher in the polysaccharide reactions than in the F II latex reaction. These normal specimens were drawn from young healthy doctors, nurses and secretaries. Those with a positive test were questioned as to recent illness such as arthralgia, hepatitis, infectious mononucleosis and unexplained sickness but no explanation for the positive test was discovered. Again these positive titres were always in low dilutions, rarely beyond 1/20.

Many of the patients in the control groups were subjected to retesting on fresh specimens,



and variability of test results was found in only one normal patient in the polysaccharide tests. It is unfortunate that a greater number of cases of rheumatic fever and diseases such as lupus erythematosus were not available to us.

#### DISCUSSION

It has been demonstrated previously that the agglutination of latex particles "sensitized" with Cohn Fraction II of pooled human globulin has a high degree of specificity for rheumatoid sera.<sup>4-6</sup> Our results with the polysaccharide sensitizing agents (as well as the series using the F II latex test) show a comparable specificity for sera from this disease. This specificity, as well as the correlation between various tests on particular patients, strongly suggests that the same peculiarity of rheumatoid serum is demonstrating itself in each case. The polysaccharide latex tests, however, show a lower titre and more frequent positive/negative variation than does the F II latex test.

It is conceivable that there is a reactant common to all these sensitizing agents. For instance, it is possible that the Cohn Fraction II of pooled human globulin contains sufficient polysaccharide to promote a reaction; it is also possible that small quantities of active globulin are present as a contaminant in the various polysaccharide preparations. The differences between these tests may thus be due to varying quantities of the active component. A definite answer to this important question will require further exploration of these tests.

Another possibility which must be considered is that the active components of the agglutination reaction are already contained in the sera, requiring only the addition of inert particles to some sera and the further addition of substances such as polysaccharides or globulins to other sera in order to bring about the reaction. The relatively high incidence of agglutination when "unsensitized" latex particles (latex only test) are added to rheumatoid serum under the experimental conditions of these tests suggests this possibility. Thus the demonstration that the polysaccharides, chondroitin sulfate, hyaluronic acid and heparin, enhance the agglutination of latex particles does not *per se* prove that they enter into a specific combination with a factor from rheumatoid serum. The fact that comparable potency in this respect is shown by a portion of pooled human serum as well as by three dif-

ferent polysaccharide substances would suggest that their effect may be non-specific as far as the underlying reaction itself is concerned. However, these polysaccharides are very closely related substances and the possibility of chemical or immunological cross-reaction between them is evident.

A number of other substances have been tested as sensitizing agents, including various polysaccharides other than the ones reported in this paper, but no positive reactions have been obtained.<sup>2, 9</sup>

It is also of interest that some preparations of Cohn Fraction II are inert in the F II latex test but can be made active by exposure to heat or to an acid pH.<sup>1</sup> It is possible that such treatment may alter the reactivity or availability of contained polysaccharides in this globulin fraction. Possibly related to these observations is the work of Smyth,<sup>12</sup> who noted a decrease in the polysaccharide content of the supernatants from hæmagglutination reactions with rheumatoid sera. He was also able to correlate sheep cell agglutination titre of rheumatoid serum with the polysaccharide concentration of the euglobulin fraction of that serum.

It would be of great significance if it could be shown that polysaccharide components of joints are capable of entering into combination with a factor or factors of rheumatoid serum. Such a reaction could be conceived as having an auto-immune basis and it would offer an attractive explanation for the chronic inflammation of rheumatoid joints. The presence, in rheumatoid serum, of muco-protein in increased amounts and the occurrence of secondary deposits of amyloid in rheumatoid disease may be related to the formation in the serum of rheumatoid patients of such protein-polysaccharide complexes.

It is of first importance, therefore, to determine whether or not these polysaccharide additives are specifically entering into combination with a factor which is peculiar to rheumatoid serum. We are at present engaged in attempts to evaluate this possibility. It has been demonstrated that rheumatoid sera contain increased amounts of euglobulin which is precipitable by the addition of chondroitin sulfate<sup>10, 11</sup> and it has been shown that chondroitin sulfate is capable of combining with various proteins.<sup>13</sup> However, the quantities of chondroitin sulfate used in these reactions are of much greater magni-

tude than are necessary to produce latex agglutination in rheumatoid serum and there is some doubt whether the reactions can be compared.

The further evaluation of polysaccharide-sensitized latex particle agglutination reactions may contribute to our eventual understanding of the etiology and pathogenesis of rheumatoid arthritis.

#### SUMMARY

Modifications of the standard latex fixation test are described in which the Cohn Fraction II of pooled human serum is replaced by the polysaccharides, chondroitin sulfate, hyaluronic acid and heparin.

Fresh sera from a group of carefully selected patients with rheumatoid arthritis and from a control group of patients were tested by the various methods described.

The polysaccharide latex tests show a specificity for rheumatoid sera comparable to the standard latex fixation test. Certain differences between the tests are discussed.

The implications of these reactions in which a factor in rheumatoid serum apparently interacts with polysaccharide components of joints are discussed.

We wish to express our appreciation of the technical assistance of Mrs. Florence White and Miss Margaret Stuckey. We are indebted to Dr. K. A. Evelyn and Dr. A. W. Bagnall for helpful criticism. We gratefully acknowledge the cooperation of physicians at the hospitals and clinics of this city in making patients available to us.

The method and results of the polysaccharide latex tests were presented at the International Congress on Rheumatic Diseases, Toronto, June 1957.

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#### RÉSUMÉ

L'emploi de l'épreuve de la fixation du latex dans le diagnostic de la polyarthrite chronique évolutive a déjà été présenté dans ces pages (*Canad. M. A. J.*, 76: 621, 1957). Les auteurs font part dans le présent article de certaines modifications apportées à la méthode de Singer et Plotz, portant sur le remplacement de la fraction II de Cohn soit par des polysaccharides, soit par du sulfate de chondroïtine, de l'acide hyaluronique ou de l'héparine. On applique ces différentes variations de la formule initiale au sérum frais d'un groupe choisi de rhumatisants; le sérum d'autres malades non rhumatisants sert de témoin. L'épreuve du latex avec polysaccharides montra une spécificité pour le sérum de la P.C.E. comparable à celle de l'épreuve originale de fixation du latex. Les différences entre les deux méthodes sont commentées dans le texte. Il est intéressant de noter les implications que contient la réaction entre un certain facteur du sérum dans la P.C.E. et les polysaccharides des tissus articulaires.

#### THE SIGNIFICANCE OF STATES OF APPARENT OR ASSUMED INTELLECTUAL INADEQUACY IN THE DIAGNOSIS OF MENTAL DEFECT

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TO DESIGNATE ANYONE as a certifiable mental defective involves a decision so serious that it can only be justified after the most careful elimination of possible alternatives. Certifiable mental defect depends on dual criteria. Not only must there be intellectual retardation from an early age, but social incompetence in one form or another must also be present. Should

an erroneous opinion be reached with regard to the first criterion, certification might then be completed on the basis of coincident or subsequent social incompetence. It therefore becomes doubly necessary to ensure that the first prerequisite is completely satisfied. To do so means consideration of intellectual inadequacy in its various forms, as well as certain specific defects of visual, auditory and speech functions which might appear to simulate intellectual inadequacy. The differential diagnosis of mental defect also takes in a number of conditions characterized by delinquent, convulsive and psychotic behaviour, but on the whole these concern more the second criterion<sup>1</sup>. When intellectual retardation is the main point at issue the first group is the more numerous and applies especially to the moron grade (I.Q. 50-70), whereas specific defects, although less common, involve conditions which

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conceivably could be confused with any grade of defect.

The degree of intellectual retardation to come within the range of feeble-minded intelligence was originally determined according to the Binet scale where an intelligence quotient of 70 represented the borderline between feeble-minded and merely dull intelligence. No hard and fast line can be drawn, however, for some adults with an I.Q. of 60 are socially competent and capable of independent existence whilst others with an I.Q. of 80 are so lacking in common sense as to be quite incapable of looking after themselves. In general, where other criteria are fulfilled, an I.Q. up to 70 presents no difficulty in certification. There is likewise a fair measure of support for extending this up to 75. Difficulty is apt to be encountered above this level but persons do exist who, despite a performance above psychometrically determined feeble-mindedness, function so defectively in social and practical situations as to require care, supervision and control for their own sake or that of others.

This difficulty therefore arises in the case of dullards, representing that section of the population whose intelligence level is immediately above the moron range. Dullards have an I.Q. variously regarded as 70 to 85, or 70 to 90. The category of dullard thus includes the group with an I.Q. of 70 to 80, sometimes referred to as borderline defective. Estimates of their numbers vary, depending on the intelligence range used as the basis of computation. On the basis of an I.Q. range of 70 to 85 one estimate places dullards at 6% of the school population,<sup>2</sup> whereas another employing the more extensive range of 70 to 90 places them at 12.9% with 4% having I.Q.'s between 70 and 80, and 8.9% between 80 and 90.<sup>3</sup>

Their rate of intellectual development is slow compared with others of the same chronological age but it is still in advance of feeble-minded children. Some dull children are capable of education in ordinary schools but others require special facilities. Gesell<sup>4</sup> distinguishes three types of case: borderline dull, borderline unstable and borderline defective, of whom the last-named approximates to moron defect. Cases like this show so obvious an inferiority of intelligence and judgment that later stability can only be ensured by the exercise of adequate supervision and training during the period of adolescence.

Not uncommonly, dull children give a spurious impression of alertness which tends to distract attention from the true nature of their insufficiency. Again the real state of affairs may not always be apparent in dullards with good emotional stability. Thus Abel and Kinder<sup>5</sup> have pointed out that some dullards are so well adjusted emotionally and so liked by their more intelligent classmates that they may attain a dominant position in their group despite their relatively reduced intelligence.

The ranks of delinquents, too, are to some extent recruited from this source. Burt<sup>6</sup> in fact has estimated that as many as 28% of juvenile delinquents are dullards. The reason no doubt lies in the fact that they are less able to profit from experience, have less foresight than the average, and are at the same time less resistant to evil influences. These characteristics they share with the feeble-minded, although not to the same extent. In a small number of cases the lack of common sense may be sufficiently obvious and the degree of social incompetence so marked that they can reasonably come within the scope of certifiable mental defect.

Failure to detect and make allowance for the subnormality of dullards may be a frequent cause of psychoneurosis, more especially in an industrial setting. Whilst there is some evidence to support the view that hysteria, for example, is more prevalent in people of dull intelligence, it is possible that increased liability to psychoneurosis may principally reflect the greater tendency for social and environmental pressures to engender emotional strain in the unintelligent.<sup>7</sup>

The dullard section of the population is important from another angle, since this group gives rise not only to dullards themselves but also to the bulk of individuals with a moron level of intelligence. It has been shown<sup>8</sup> that in any family the intelligence of the progeny normally varies within a range of plus or minus 15 of the highest and lowest parental intelligence quotients. Since the tendency of like to marry like is particularly noticeable in the realm of intelligence, it is clear why dullards contribute so significantly to the numbers of the feeble-minded.

Equally to be distinguished from certifiable mental defect is intellectual retardation without social inadequacy. This is comprised of persons of moron intelligence who nevertheless have sufficient social competence to keep them from

coming within the scope of the Mental Deficiency Acts. Generally speaking, the designation implies stable conduct, ability to look after themselves reasonably well, and the absence of obvious antisocial tendencies. Where children of school age are concerned the alternative term, educationally defective, is sometimes used. In Great Britain, for example, the educationally defective are included along with the dull and backward within the category of educationally subnormal pupils. As such they qualify for education in special classes and schools under the education authorities. In general, children whose defect is predominantly intellectual rather than social, and whose I.Q. ranges from 70 down to about 55, are able to qualify. Children at the lower end of the scale who cannot be taught to read or spell simple words of one syllable, add and subtract units, or make progress in manual subjects are not regarded as suitable for this type of education.

Even before leaving special school a proportion of pupils will have demonstrated their ability to develop into useful citizens whilst others will have already made clear by their social failure that they require care, supervision and control for their own sake or for that of others. Such patients, as well as those who later develop antisocial tendencies, will qualify for certification as mental defectives.

In adult life many intellectually retarded people whose social competence is fair are to be found employed as domestics or engaged in the simpler and more routine aspects of industrial work. In these lowlier posts they may even have an advantage over workers of superior intelligence because of their reduced liability to suffer boredom in monotonous repetitive work. Quite a considerable number are able to establish themselves in the community and as many as two-thirds manage to retain suitable employment. A recent follow-up of ex-pupils from special schools showed that 61% were successful whilst a further 11% were partially successful.<sup>9</sup> For the maintenance of this happy state of affairs, however, factors other than industrial play a considerable part. In many instances the adjustment of these people depends on continuance of the stable and sympathetic environment provided by parents, wives and understanding employers. When deprived of this support they are often, as McCalman<sup>10</sup> has pointed out, just as likely to become unstable and bewildered as

certified mental defectives. Aside from total breakdown they may become a liability to the community from neurotic illness, the true nature of which is not always immediately clear. According to Elster,<sup>11</sup> failure to recognize individuals of this type may lead to costly and unnecessary specialist examinations and even to the awarding of unjustifiable compensation.

The remaining condition in this group which occasionally enters into the differential diagnosis of mental defect is backwardness or educational retardation. Backwardness is a term reserved for children whose educational attainments have fallen below the level of their natural abilities. Scholastically they are defined by Burt<sup>12</sup> as children who "in the middle of their school career would be unable to do the work of the class next below that which is normal for their age." On the Terman-Merrill scale they have I.Q.'s within the average range, with rather more under the hundred mark than above it. Their poor scholastic record may breed suspicion of feeble-mindedness, more especially when behaviour disorder is associated. Whilst backwardness is due in some cases to a milder degree of intellectual subnormality than occurs in dullards, it is due entirely in others to remediable causes. Generally speaking, the handicaps leading to backwardness are many and varied, including such widely different conditions as chronic illness, mild visual defects, frequent change of school, lack of drive and specific arithmetical disability. In their elucidation and treatment the educational psychologist is likely to play as important a part as the physician or psychiatrist.

Specific defects impairing the visual, auditory and speech functions form a small but important group. Children affected in this way may appear only backward when the degree of handicap is slight, but where it is severe they run a grave risk of being thought feeble-minded.

This suspicion can arise in regard to children blind from birth or early infancy. In some cases quite a degree of retardation does result from sensory deprivation, and the matter is further complicated by the fact that failure of an infant to respond to visual stimuli occurs as well in some instances of feeble-mindedness where there is an associated oculomotor retardation. Later, blind children tend to show considerable slowness in educational achievement, sometimes as much as two years compared with sighted child-



ren of the same chronological age. This is understandable in view of the loss of a critically important channel of information. An impairment of this nature underlines the need for special training at the earliest opportunity—a need which applies with equal force to congenitally deaf children—in order to prevent the development of a severe degree of retardation. Blind children can be tested by means of special intelligence tests like the Hayes modification of the Binet scale, but in some instances the exclusion of feeble-mindedness may only be possible after prolonged observation and careful scrutiny of the developmental history.

A related difficulty may be encountered in the impaired macular vision which results from visual cerebral injury. Such partially blind children are able to see only in a blurred and fleeting fashion with their peripheral vision. The attempt to fixate soon brings on visual mannerisms like head-tilting. Strabismus, incoordinated eye movements and pallor of the optic discs are usually present. At the same time there is almost always injury to the motor areas with some manual disability. It is hardly surprising that the mental level should be suspect, yet in spite of an adverse start many of these children are said to do remarkably well from a developmental standpoint. Gesell<sup>4</sup> in fact stresses the need for caution before pronouncing adversely during the earlier years.

The disability in schoolchildren which is perhaps most likely to be confused with feeble-mindedness is congenital word blindness or developmental alexia. These are terms subject to different interpretation by different writers, but if developmental alexia, as employed by Brain,<sup>13</sup> for example, should prove the more generic expression, congenital word blindness would still refer to the more severely afflicted patients where in any case the mental level is likely to be most suspect. Before going to school the child is generally regarded as normal in every way and it is only afterwards that the specific reading disability shows itself. Inability to identify, understand and reproduce the written symbol soon brings about a slowing up in academic progress. In the severest cases the victim may not even be able to recognize the letters of the alphabet. More usually the disability shows itself in the characteristic reversals affecting letters, syllables or words. In the case of letters reversal may be in the lateral or vertical orienta-

tion; reversal in the lateral orientation is more common, with confusion between b and d, and p and q, but vertical orientation may also be affected, with inability to distinguish between n and u and p and b. Reversal of syllables, such as BRUNT for BURNT, and of small words, like SAW for WAS, is equally characteristic. In one degree or another it has been estimated that about 10% of readers are affected. Apart from the reading disability itself the frustration and discouragement engendered by it may result in anxiety, loss of interest and even behaviour disorder, thus further increasing the risk of confusion with mental defect. Gallagher<sup>14</sup> is of the opinion that this specific disability should be considered in every case of scholastic failure. On the other hand Mayer-Gross and his colleagues<sup>7</sup> have pointed out that all the more important literature in this subject has dealt with English-speaking children and they have surmised that in other languages such as the Romance group phonetic spelling and writing make the acquisition of reading much easier. However, Roudinesco and Trélat,<sup>15</sup> dealing with French-speaking children, have analyzed 42 personal cases. The distinction from mental defect can usually be made on the typical reversals, the history of normal development and a valid intelligence test, a wide scatter tending to occur in specific reading disability.

Deafness and partial deafness cannot be dismissed from mind when feeble-mindedness is in question, particularly since the incidence of these conditions is known to be increased in mental defectives. Johnston and Farrell<sup>16</sup> found from their investigations that hearing loss was approximately five times as great in defectives as amongst public school children of comparable chronological ages. Where the mental level was in doubt they advocated transfer to a school for the deaf to obtain the specialized training not generally available in institutions for mental defectives. If the degree of retardation should prove too great to permit of education in the school for the deaf, the final decision for placement in a mental deficiency institution would then rest with staff thoroughly experienced in the behaviour of deaf and partially deaf children.

Loss of environmental stimulation brings about effects which are as apparent in the congenitally deaf as they are in the congenitally blind, and indeed some residual retardation

may persist. Again as in the parallel case of blindness diagnosis is complicated because some defectives show a delay in responding to sounds, or again both deafness and retarded intelligence may be present.

More likely to be overlooked is the condition of high-tone deafness with its selective impairment of higher frequencies. According to Hardy,<sup>17</sup> a mistaken diagnosis of feeble-mindedness is more apt to be made in children with less severe impairment than in those with profound hearing loss. Speech in high-tone deafness is loud and toneless and shows faulty appreciation of the higher pitched components. Consequently sounds such as "s, z, f, t, th" are either omitted or confused. The effects of this selective and often unsuspected deafness are to be seen in lack of attention, defective speech and faulty spelling. The underlying fault becomes apparent in these cases following audiometric examination.

The greatest risk probably occurs with regard to children whose peripheral hearing is intact but who have suffered impairment in the capacity to comprehend speech or sound. No fewer than three conditions, fortunately uncommon, may be responsible. These are congenital word deafness or receptive aphasia, auditory agnosia, and central aphasia. The child with word deafness can appreciate ordinary sounds but fails to appreciate the significance of words. He pays no attention to what is said to him, and speech if present at all is in the form of an idioglossia. Older patients may learn to compensate for their specific defect by lip-reading: in such an event the uttering of instructions behind the patient's back reveals his dependence on this mechanism. Auditory agnosia is more severe in its effects. It has been stated that in children this condition does not occur without simultaneous receptive aphasia.<sup>18</sup> In their case, therefore, there is inability to comprehend the meaning of all sounds, both verbal and non-verbal, even though it is clear that affected children are able to note the presence or absence of sound. In central aphasia with its severe disturbance of inner language functioning there is inability to use language for any purpose. According to Myklebust<sup>18</sup> this grave disorder is more common in children and is expressed clinically by complete inability to behave symbolically. Myklebust has stressed the value of behavioural symptoms in the diagnosis of these conditions.

Although dealing more especially with receptive aphasia, he points out that these symptoms are also useful in auditory agnosia and central aphasia. Amongst other characteristics he lists failure to use vocal capacities, such as they are, in order to influence others, deficiency or absence of gestures, poor listening behaviour, lack of shyness, lack of intensity in emotional expression, and retarded social maturity especially in communication, socialization and motor areas. Failure to observe such criteria has without doubt led on occasion to a diagnosis of mental defect.

Absence of speech may occur apart from any hearing impairment or auditory imperception. In this connection feeble-mindedness is more apt to be suspected in delayed development of speech, congenital motor aphasia and certain types of mutism.

The onset of speech may be greatly delayed in subjects who represent the extreme gradient on the slope of normal development of this faculty. The afflicted child may not utter a word until he is four years of age or even older. Since the age of onset of speech is popularly regarded as indicating the child's later development, any marked delay is looked upon with apprehension, and justifiably so. Thus out of 1000 children studied Morley and her colleagues<sup>19</sup> found four at the age of six years with delayed speech, and of those significantly enough three were ascertained to be feeble-minded. A delay of benign type in the development of speech appears to be hereditary and there is generally a family history showing that parent or grandparent did not talk until the age of four years or even later. In any case the child whose speech is delayed from this cause is likely to have passed his other milestones at the normal time.

Like the foregoing, the child with congenital motor aphasia can fully understand what is said to him. He cannot, however, articulate clearly and even when he can form individual consonants he is still unable to link them into words. According to Orton,<sup>20</sup> a child with this type of aphasia is quite capable of recognizing his errors in articulation. Here again lack of understanding and frustration may lead to behaviour disorder, thus heightening the superficial resemblance to mental defect.

A further possible cause of referral is mutism, which may be of hysterical, elective or psychotic type. Hysterical mutism is apt to develop



in susceptible children whose parents are either overprotective or else have tried too soon to force the child to talk. The child makes no effort to speak and the condition is distinguished by complete absence of every phonated word and sound. In elective mutism, on the other hand, the child is ordinarily able to speak but remains mute under certain conditions. This type of mutism is usually precipitated by physical illness in sensitive children from insecure homes, and the absence of speech is manifest only in the presence of particular individuals. According to Salfeld,<sup>21</sup> it represents a protective mechanism directed against these individuals. When, as often happens, mutism is expressed at school it is hardly surprising that doubt should be entertained with regard to either intelligence or sanity. Finally there is the mutism which occurs in frank psychosis. The mutism of ordinary schizophrenia might occasionally crop up, but much more likely to be referred is the child with the mutism of infantile autism. Kanner<sup>22</sup> and other writers have underlined the danger of wrongly labelling autistic children defective. According to Kanner their outstanding peculiarities are a profound withdrawal from contact with people, an obsessive desire for the preservation of sameness, a skilful and even affectionate relationship to objects, the retention of an intelligent expression, and either mutism or language unsuitable for interpersonal communication.

#### SUMMARY

Certifiable mental deficiency depends on the twin criteria of intellectual retardation and social incompetence. In satisfying the former criterion it is necessary to consider two groups of conditions. On the one hand there are states where intellectual inadequacy is present, either of the same magnitude as in mental defect or of lesser degree, but which do not possess the same grave significance. This group includes cases of intellectual retardation without social incompetence, dullness and backwardness. On the other hand there exist specific defects of visual, auditory and speech functions where suspicion of intellectual retardation might readily arise if insufficient allowance is made for their presence. The nature of these varied conditions is briefly discussed.

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#### RÉSUMÉ

Le diagnostic de déficience mentale peut souvent sauter aux yeux, mais en d'autres circonstances, il présente des traquenards que le médecin averti doit savoir éviter. Le placement des déficients mentaux est fondé non seulement sur l'arriération mentale mais aussi sur la dépendance sociale. La zone frontière du quotient intellectuel aux environs de 70 comprend la grande majorité des cancrs dont le sort soulève des problèmes sociaux. On a déjà prétendu que 28% des délinquants juvéniles sortent de ce groupe. Cette partie de la population en procréant des êtres semblables à eux-mêmes contribue à grossir les rangs des faibles d'esprit.

L'enfant arriéré peut donner une fausse impression d'intelligence. Certains lourdauds sont si bien équilibrés au point de vue émotif qu'ils excitent l'admiration de leurs camarades intellectuellement mieux doués, mais instables. Les classes de perfectionnement permettent à certains débiles de mener, un jour, une existence indépendante. Une enquête a montré que 61% des anciens élèves de ces écoles s'étaient adaptés d'une façon satisfaisante; cette adaptation dépend beaucoup du milieu sympathique et stable dans lequel le débile pondéré peut évoluer.

L'inadaptation scolaire est heureusement due en grande partie à des causes rémédiabiles. Le retard dans le développement linguistique n'est pas toujours attribuable à la déficience mentale. Il peut être simulé par des déficiences de la vue et de l'ouïe. L'auteur cite comme autres causes possibles l'alexie, la dyslexie, la surdité aux fréquences élevées, l'aphasie centrale et réceptive, et l'agnosie auditive.

#### SIMPLE HELIUM METHODS FOR MEASURING RESIDUAL AIR

The simplicity, the speed of obtaining the measurements, and the reproducibility of the helium method, along with the accuracy demonstrated by comparison with the oxygen open-circuit method, make this a desirable technique. The helium equilibration time is of value as an index of air distribution in the lung, and compares favourably with the alveolar nitrogen determination by the oxygen open-circuit method. The helium method simplifies accurate quantitative residual air measurement with minimal expense.—H. L. Motley, *Am. Rev. Tuberc.* 76: 601, 1957.

## THE PROBLEM OF THE SECONDARY GAIN PATIENT IN MEDICAL PRACTICE\*

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THIS PAPER is presented for the distinct purpose of focusing attention upon the insidious development of the compensation problem in the practice of medicine. Time was when this was fondly considered to be limited to the field of the pension medical examiner with the Department of Veterans Affairs, and the insurance doctor, but this is no longer the case. As the so-called "welfare state" advances and sick benefits, insurance schemes and pension plans increase in number and complexity, so must the capable physician know more about the individual who, for unconscious reasons, will perpetuate the symptoms of an illness for secondary gain.

The personality of the individual so motivated will be examined briefly.

It is true that everyone who becomes ill or injured becomes, for a time and to a degree, more dependent upon others. There are, however, wide individual variations in the personal acceptance of this state of affairs. The well-adjusted person must accept an illness or injury, and permit himself to regress to a rather passive state and let himself be taken care of, with psychological equanimity. It is as if he says, "I am sick and will accept help as long as I need it and I will get better." This attitude permits the well-adjusted person to fall back on earlier proven and satisfying patterns of allowing others to care for him, since to do so is not threatening or anxiety-producing. It threatens neither feelings of manhood nor of womanly integrity, as the case may be; nor is the patient full of fear that if rendered helpless no one will love or care for him.

In contradistinction to this, a person may have unrequited demands for love or attention

going back to the formative years of life, which are symbolically reawakened by the current situation. As a result of past frustrations in these areas, the patient may be more or less uncertain of his own adequacy or competence. These doubts are usually operative in whatever biological and social roles he is supposed to fulfil. He may feel that despite all his striving he cannot earn or merit recognition and the necessary amount of care from his family and his entourage.

One could summarize by saying that one's personality enters into both sickness and health. The well-adjusted person copes with sickness, as with health, relatively well; whereas many persons with neurotic conflicts develop anxieties and fears, and become uncertain and indecisive.

The matter of secondary gain will now be considered in the light of the above statements. Secondary gain may be defined as the psychological and sociological advantages obtainable through being ill. Although some of the motivation for secondary gain may be on a conscious level, most of it is unconscious. It is safe to say that the unconscious factors are always present and are always powerful. What the patient obtains from being ill may be very obvious to an outside observer, but is usually not apparent to the patient. Sometimes the secondary-gain factor is so subtle that it is recognized only with great difficulty by the physician. This occurs when the physician is unaware of the existence and the significance of the underlying psychological factors.

Thus, in patients who use illness or injury for secondary gain, their symptoms can be visualized as expressing the feeling, "It is not my fault that I am weak; it is my injury (or illness). This is what stops me." Here the reality of an injury or illness is used to excuse and justify the already existing feelings of inadequacy, of personal inferiority and worthlessness that have existed for years. The disability is then used to justify the overt appearance of the need to be passive, and to be cared for, as well as for the avoidance of competition. Before the injury these feelings were present but were not acceptable to the patient's conscious morality, since in our culture it is agreed that "a man is supposed to compete, work, take care of his family, etc." With an injury or illness the above material can be allowed to appear without guilt since "It is not my fault."

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These factors can operate in various spheres of life. Thus, they can be used to avoid, or minimize contact with, some area of life that is dangerous and threatening. The timing of an illness is often significant. An example follows:

The assistant manager of a business firm is promoted to manager just after he has sustained a relatively insignificant injury to his back. He is desperately afraid of the added responsibility but this must remain a secret which he avoids admitting clearly even to himself. As his physical disability is maintained, he may further avoid looking at his feelings of inadequacy and thus can "forget". Instead, he protests to the orthopaedic specialist his discouragement and disappointment at not being able to accept the promotion.

A careful background study often reveals indications of pre-existing unconscious manipulations of a smaller degree, provided this history is taken before the physical symptoms become fixed. After this, the patient must perforce adopt an attitude of denial with respect to his personality defects.

Another type of secondary gain in which a threatening situation is avoided is often seen in medical practice. An example of this is the wife who has marked conflicts over sexuality, and develops a violent headache or other well-timed symptoms, which force her to take to her bed with sedatives or analgesics when she sees her husband's sexual interest mounting. She is thus too ill for sexual relations. Similar behaviour is often seen in the male.

Many criticisms and witticisms have been aimed at psychiatry for its underscoring of the significance of sex as a cause of conflicts and emotional upsets. The truth is that this instinctual drive is of the utmost importance, and anyone who believes the contrary is simply playing games with his thinking.

In the examples just given, failure to recognize the largely unconscious elements present leads to difficult problems for the treating physician. All too often the doctor finds no organic lesion of sufficient degree to explain, or justify, the degree of impairment or disability complained of. It is vital to the understanding, and therefore management, of the patient that the physician realize that the patient is totally or largely unaware of his own unconscious manipulations of the illness, and what he is obtaining from it. There are exceptions to this and they will be dealt with shortly.

In their everyday lives many of the above patients attempt to demonstrate—sometimes successfully—a degree of stability which is the antithesis of their underlying feelings of inadequacy and insecurity.

This brings us to the problem cases which are the bane of industrial physicians, army medical officers, compensation boards, and pension examiners. These are the patients who, after an illness, wound, or injury, seem to consciously exploit their symptoms in a deliberate and calculating way in the hope of obtaining as much available money as possible. It is an apparent paradox that, despite being so helpless in terms of social and occupational integration, some of these patients show great energy and activity in pursuit of remuneration. Here again these patients can only be understood when the unconscious, psychological meaning of being disabled on the one hand, and of the reassuring, unconscious meanings of money on the other, are evaluated in terms of their personal psychology.

Money, of course, has a real value. It is not the patient's imagination that makes him realize this. Yet his use of money symbolizes more than its utilitarian significance. The symbolic use of money as a visible evidence of "compensation" is something quite apart from its social value as a means of obtaining material things. Here money is not just money, but is a tangible balm for injuries or hurts suffered—both the real ones in the accident, wound or injury, and the unconscious psychological ones at the hands of his past masters in the family group. It is a way of soothing old hurts; it is a visible expression of society's acceptance of responsibility for his state. It is proof of weakness, but of an acceptable status, and as such is a socially accepted excuse for impairment or inadequacy, as well as proof positive that "someone has to take care of me for what was done to me in the past." It soothes angry feelings and ruffled feathers, and its vigorous pursuit is evidence of the intensity of the patient's angry feelings about life's injustices and hurts. This type of case is not understandable if one does not evaluate these factors.

As to the patient's choice of symptoms, the following seem important. Probably as a result of increased knowledge of anatomy, physiology and endocrinology, the man on the street no longer has recourse to symptom pictures so obviously impossible that the physician easily

"catches him out". He now complains of low-back pain, of headache, of stomach symptoms, or of chronic fatigue. Not infrequently he has absorbed the symptoms of some medical condition he unconsciously mimics in his need for a solution to his inner conflicts. The physician, therefore, is often faced with a more sophisticated and subtle diagnostic problem than heretofore.

The physician dealing with patients, whether in the Army, in the Department of Veterans Affairs, in industry, or in daily medical practice, must be aware that illness or injury can be used to gratify largely unconscious needs. These factors may be moderate or minimal, or loom very large in the clinical picture. The importance of the need for gratifying dependency, for self-justification, for reinforcement of an underlying need for passivity without having to feel guilty about it; and of the use of illness to justify avoidance of difficult life areas, is stressed. The importance of money as a symbol in these terms must be recognized.

At this time in the history of our society, encouraged by our health security measures, a person may attempt to translate his needs for psychological protection into the realm of monetary rewards; that is to say, he looks for a pension. Since the majority of these individuals are basically rather conscientious, honest people, many of them cannot permit themselves to work at all if they believe they are incapacitated. They are often so meticulously honest that if they receive a 75% pension they can permit themselves to work only 25% of the working day. This becomes even more interesting and significant when the patient reasons that perhaps he is not well enough to function to this degree, and demands a 100% pension.

Although a variety of psychiatric diagnoses may be made on these patients, the majority of cases fall into the categories of the passive-dependent personality with conversion hysteria, and the schizophrenias. The type of conversion symptoms may, however, be rather complex, as already described. The schizophrenias are often not readily recognized, since they are usually in an early form and to a great degree masquerade as something else. Occasionally, psychological tests (projective techniques) are of considerable value in helping to establish this difficult diagnosis.

What is the practical method of coping with this problem, and at the same time maintaining the attitude of the good physician? While there is no straightforward and simple answer, it is fortunate that some past experience may point the way. Certainly, if compensation in the form of a pension must be instituted, this should be arranged with a minimum of delay and should be as fair as possible. In addition, the decision should be made in as irrevocable a form as possible; that is to say, every safeguard should be set up to prevent the subject from anticipating further remuneration through his illness. This is not always feasible since all too often there is an actual increase in disability with the passage of time. Nevertheless, this should be the general policy. In two contiguous areas of Europe following World War I, the applicants for pensioning on psychiatric grounds were dealt with in opposite ways. In one area, the applicants were given a lump sum as indemnity, with little opportunity for appeal later. In the other area of the country, the applicants were placed on a pension in the form of an annual income. The results were very interesting when reviewed after the lapse of a number of years. In the part of the country where a lump sum had been the method of compensation, some 90% of the patients were working; in the other group 90% were unemployed.

The Canadian Pension Commission has established the attitude that the subject of a neurosis does *not* receive a pension except very occasionally, and only then after the case has been thoroughly considered by a special committee. One might say that the subject of a neurosis is looked upon in a different way from other sick people. This may be true, but physicians should not be guilty of assisting the patient to remain ill through the payment of a monthly sum of money. This would reinforce his neurotic difficulties. It may well be that some people are penalized by this policy, but it must be kept in mind that this over-all policy is much more productive of good mental health than the opposite scheme would be.

This paper has been written because few of the problems involving secondary gain can be referred to the psychiatrist. There are just not enough psychiatrists available and, even if there were, it is not certain that referral of the average compensation case would be justifiable. Furthermore, secondary gain is seen in every branch



of medicine and is not limited to pension problems. Thus, every physician is forced to deal with them, and the majority of cases are dealt with by the non-psychiatric practitioner. The family doctor who sees the patient in his natural milieu, and who trains himself to look at the total constellation of factors operating in the patient's life, is often the one who can detect the significance of the patient's symptoms before they crystallize into a fixed pattern of thinking and behaviour.

It is hoped that the presentation here of several of the important psychological considerations seen in these problems will help make these patients understandable, and thereby aid their treatment and management.

#### PRIMARY SUTURE OF THE COMMON BILE DUCT COMPARISON WITH CASES TREATED BY STANDARD METHODS

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AFTER EXPLORATION of the common bile duct, the common practice is to drain the duct either by a Kehr's T tube or by a capillary rubber tube. That this is not universally accepted as necessary is seen by many reports from Australian, European and American authors.

Many of these writers believe that primary suture of the duct with drainage of the field of operation is satisfactory and safe (Richter and Buchbinder,<sup>10</sup> Bakes,<sup>1</sup> Miller,<sup>6</sup> Beall,<sup>2</sup> Edye,<sup>3</sup> Pettinari,<sup>8</sup> Mallet-Guy and Gangolphe<sup>4</sup>). Jaundice is suggested as the indication for drainage by one writer (Mayo<sup>5</sup>) and another (Mirizzi<sup>7</sup>) lists the criteria for primary suture of the duct as patency of the common bile duct, removal of all stones and the presence of a normal pancreas.

The mortality for the operation of choledochotomy and primary closure of the duct is variously quoted as 7.5%<sup>9</sup> and 2.6%.<sup>3</sup>

The purpose of the present paper is to report a series of cases of choledochotomy with primary

#### RÉSUMÉ

La connaissance de l'hystérie et de ses gains secondaires déborde le domaine de la médecine militaire et industrielle ainsi que celui des bureaux de dédommagement ou de pension, et pourrait bien toucher de près la médecine générale vu l'imminence possible, selon les auteurs de ce présent article, de l'étatisme médical. Retranché dans sa lésion, l'hystérique ne voit pas son intégrité sexuelle compromise et il peut même réclamer des égards et des manifestations d'affection qu'il n'obtiendrait pas autrement. Son état lui procure des avantages psychologiques et sociologiques indéniables. Sa lésion sert de bouc émissaire et lui permet de donner libre cours à ses sentiments d'infériorité, d'incompétence et d'insuffisance sans soulever chez lui aucun remord. L'argent qu'il peut ainsi obtenir ne compte pas tant à ses yeux par son pouvoir d'achat que par le redressement tangible d'un présumé tort qu'il aurait subi. La vulgarisation des connaissances médicales rend la symptomatologie du pithiatique beaucoup plus subtile qu'elle ne l'était jadis. La schizophrénie peut offrir un tableau clinique qui ressemble de très près à celui de l'hystérie. Il semble entre autres mesures que le règlement précoce et définitif de tous points en litige soit une manière efficace de supprimer les accidents pithiatiques.

suture, to comment on the early and late results, and to compare these with a series treated by standard methods.

#### MATERIAL

One hundred and sixty cases of disease of the biliary tract were operated upon in one surgical unit at Oldchurch Hospital, Romford, Essex, England, between 1948 and 1952 (Table I). In 82 of these cases choledochotomy and primary suture of the duct was performed by the standard technique. In each case a malleable probe was passed through the ampulla of Vater into the duodenum. The incision in the duct was closed with fine catgut and a drain placed in Morison's pouch. The operative findings were as follows: stones in common duct, 31; negative exploration, 51.

#### EARLY RESULTS

There were two postoperative deaths, one due to pulmonary embolism on the ninth day, unfortunately not confirmed by postmortem, and the other on the second day. Autopsy showed the presence of bronchitis, emphysema and cor pulmonale.

There was leakage of bile round the drain for several days postoperatively but this usually ceased by the sixth day. In one case there was

TABLE I.

Operation	Females	Males	Total	Mortality	Stones in gall-bladder only	Stones in gall-bladder and duct	Stones in duct only	No stones
Cholecystectomy.....	68	5	73	—	58 (79.5%)	—	—	15 (20.5%)
Cholecystectomy and choledochostomy.....	3	—	3	—	—	3	—	—
Choledochostomy.....	1	—	1	—	—	—	1	—
Cholecystectomy and choledochotomy.....	68	12	80	2 (2.4%)	47 (58.5%)	29 (36.2%)	2 (2.5%)	2 (2.5%)
Choledochotomy.....	2	—	2	—	—	—	1	1
Cholecystostomy.....	1	—	1	—	1	—	—	—
Totals.....	143	17	160	2 (1.2%)				
Sex ratio—8.4 : 1								

a biliary fistula which did not close until the 17th day. Her condition was satisfactory when followed up.

All but six patients were discharged from hospital within 21 days. The discharge of three patients was delayed because of wound infection and disruption, and two more suffered from pulmonary complications. The longest stay in hospital was 31 days and the average was 14 days.

#### LATE RESULTS

After a period of one to four years after operation, a questionnaire in the following form was sent:

1. Have you had any further operations for gall-bladder trouble?
2. Have you had a recurrence of symptoms such as you had before operation?
3. Are you satisfied with the results of the operation?

Seventy-seven (98%) of the 80 surviving patients replied or were traced. One had died of a cerebrovascular accident within a year of operation. The findings of the questionnaire are summarized in Table II.

TABLE II.

Series	Further biliary tract operation		Residual symptoms	Satisfied	Total
Romford	Yes	Nil	15 (18.2%)	75	77
	No	77	62 (81.8%)	2	77
Dundee	Yes	3	13 (20.3%)	62	64
	No	61	51 (79.7%)	2	64

It will be seen that although 15 patients had residual symptoms, only two of them were dissatisfied with the result of the operation and

in no case had a further operation been necessary at the time of the follow-up.

Of these 15 patients with residual symptoms 14 were interviewed. Their symptoms are summarized in Table III. Ten of the 14 cases were thought worthy of further investigation and in nine of them intravenous cholangiography was performed. Three of these examinations were unsatisfactory because of technical errors in radiography, and six showed normal outlines of the ducts. Five barium-meal examinations were performed and one patient was found to have a duodenal ulcer; in the rest the findings were negative.

TABLE III.—RESIDUAL SYMPTOMS IN 14 CASES

Possible biliary colic .....	2
Epigastric discomfort .....	6
Flatulence .....	6
Heartburn .....	6
Aversion to fatty foods .....	3

#### CASES TREATED BY STANDARD METHODS

During the years 1947-52 inclusive 107 explorations of the common duct were performed in Dundee Royal Infirmary and Maryfield Hospital, Dundee, Scotland. Of these patients 19 (17.6%) died in hospital. Jaundice was present at the time of operation in 40 patients, of whom 13 (32.5%) died. In each case after exploration of the duct, drainage was established by either a T tube or a capillary rubber tube. The operative findings were: stones in duct, 67; stricture, 1; negative exploration, 40.

The tube was removed on the average on the 13th day, and the average time in hospital was 22 days. Eighty-nine patients were sent a questionnaire. Ten had died since discharge from hospital, 15 did not reply and 64 replied.

Three patients had further explorations of the common bile duct. The first was five weeks



later on account of recurring attacks of jaundice, and the others were 11 months and six years afterwards respectively. Two of the patients are in a satisfactory state now but one has residual symptoms. The results of the follow-up of the 64 patients who replied to the questionnaire are summarized in Table II. It will be seen that three cases required further exploration of the common duct and that 13 patients had residual symptoms. This latter number is similar to the Romford series. The writer has emigrated to Canada, so that it was not possible to trace the 15 who did not reply to the form or to interview and investigate the cases with residual symptoms, as was done in the Romford series.

#### DISCUSSION

The thesis put forward on the basis of these results is that, as a rule, drainage of the duct after choledochotomy is unnecessary. It is usually thought desirable to drain the duct to avoid extravasation of bile and biliary peritonitis. While leakage of bile is usual and variable in amount, peritonitis did not occur in this series. There is thought to be a danger of stricture of the duct if it is sutured, but this has not been observed although it might occur if an attempt was made to obtain a watertight closure by using more than a single layer of sutures.

When the duct is not drained, routine post-operative cholangiography cannot be performed, but this is less important now that intravenous cholangiography is available. Although no case in the present series has required a second operation on the common duct so far, the writer has explored a duct elsewhere on two occasions and found no difficulty in displaying the duct at the second operation, so that the presence of the tube as a guide should a stone be left behind is not sufficiently important to necessitate a tube in the average case. It is likely that there will be fewer adhesions at a second operation when a tube has not been used. The writer does not believe that drainage of the duct is necessary to prevent hepatic failure, but as only five of the series were jaundiced at operation no conclusion can be reached from this series. However, the duct appears to decompress itself through the suture line when the pressure rises in the first few days due to oedema of the sphincter of Oddi.

The Romford and Dundee series are not strictly comparable, as the policy regarding ex-

ploration of the duct was different. In the former series this was undertaken in a much higher proportion of cases than in the latter, with the result that there were more seriously ill, poor-risk and jaundiced cases in the latter. However, making allowance for this, choledochotomy appears to allow the patient to be discharged earlier, as the average length of stay was 12 and 22 days respectively.

While it was not possible to interview the Dundee cases with residual symptoms to compare them in detail with the Romford ones, at least there seems to be no great morbidity due to suture of the duct. Neither of the two deaths appears to be due to the method.

None of the Romford cases has had to be re-explored. A second operation was necessary in three of the Dundee cases.

#### SUMMARY

In 82 cases of choledochotomy primary suture of the common duct was carried out. The mortality, morbidity and late results compare favourably with the drainage operation.

My thanks are due to Mr. E. B. Whittingham for suggesting this investigation and allowing me to perform some of the operations; to the Consultant Surgeons, Dundee Royal Infirmary and Maryfield Hospital, for permission to review their cases; to Professor D. M. Douglas for advice and criticism in preparation of the paper; to Dr. J. M. Stewart for the radiographic investigations; and to Miss Esplin for secretarial assistance.

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#### RÉSUMÉ

L'usage du tube en T n'est pas universellement considéré comme nécessaire dans la chirurgie des voies biliaires. Plusieurs auteurs se contentent de suturer le cholédoque et de drainer le champ opératoire. Dans une série de 160 cas du service de chirurgie de l'Hôpital Oldchurch à Romford (Angleterre), 82 cas furent ainsi traités. Les suites post-opératoires et les résultats à longue échéance sont analysés et comparés à ceux d'une série de 107 interventions pratiquées à l'Infirmerie Royale et à l'Hôpital Maryfield de Dundee, d'après les méthodes habituelles. Les chiffres cités semblent indiquer que le drainage du cholédoque ne soit pas une mesure indispensable et que les risques de rétrécissement du canal après suture aient été exagérés. L'absence du tube peut diminuer la formation d'adhérences et faciliter ainsi toute intervention ultérieure.

## SHORT COMMUNICATIONS

PARTICIPATION OF THE  
ADRENALS IN THE PRODUCTION  
OF RENAL AND CARDIAC  
LESIONS BY COLD\*HANS SELYE, M.D., *Montreal*

ACCORDING to the theory of the "diseases of adaptation", certain maladies are due more to a derangement of fundamentally useful, adaptive reactions to pathogens than to the direct effects of the latter.<sup>1</sup> One of the most widely discussed experiments among those which formed the basis of this concept was the finding that, when rats were sensitized or "conditioned" to mineralocorticoid overdosage (by unilateral nephrectomy and NaCl supplements), they developed nephrosclerosis, hypertension, myocarditis and periarteritis nodosa of the heart; that is, changes quite similar to those obtained by overdosage with mineralocorticoids (e.g., desoxycorticosterone).<sup>2</sup> These observations have been confirmed and extended in other laboratories.<sup>3-5</sup> It must be kept in mind, however, that the participation of the adrenals in the production by cold of renal and cardiovascular changes was suspected only on the basis of indirect evidence, namely: (1) the resemblance between the syndrome produced by cold and that elicited by desoxycorticosterone; (2) the fact that unilateral nephrectomy and NaCl sensitize for the production of this syndrome, be it elicited by cold or by desoxycorticosterone, and (3) the production by cold of marked enlargement of the adrenal cortex, simultaneously with the induction of lesions in the cardiovascular system and the kidney.

In order to prove adrenal participation in the production of such morbid changes, it would have been necessary to show that adrenalectomy prevents their production by cold. This would have been difficult when our original observations were made. Without substitution therapy, adrenalectomized animals do not withstand prolonged exposure to cold and we could not have maintained them with the only forms of therapy available at that time, i.e., desoxycorticosterone or the adrenocortical extracts. Either of these materials, in itself, produces cardiovascular and renal changes, because desoxycorticosterone is a potent mineralocorticoid and the extracts contain both glucocorticoid and mineralocorticoid hormones.

In view of the great theoretical importance of demonstrating adrenal participation in the production of cardiovascular and renal diseases by a stressor, such as cold, we have now re-

peated this work on adrenalectomized animals maintained exclusively with a glucocorticoid (cortisol). As will be seen, we found that, under these conditions, the nephrosclerosis, myocarditis and cardiac periarteritis nodosa that normally occur during adaptation to cold are prevented by adrenalectomy.

## MATERIALS AND METHODS

Sixty female Sprague-Dawley rats, with an average initial body weight of 100 g. (range: 94-106 g.), were subdivided into four equal groups. In all animals, the right kidney was removed under ether anaesthesia, through a subcostal incision, on the first day of the experiment. After this, the animals were given 1% NaCl instead of tap water to drink, since unilateral nephrectomy and NaCl supplements notoriously sensitize the rat for the cardiotoxic and nephrotoxic effects of mineralocorticoids.

Group I acted as controls and were kept at room temperature (about 25° C.) throughout the experiment. Group II were exposed to cold. Group III were exposed to cold and treated with cortisol acetate (COL-Ac). Group IV were exposed to cold and treated with COL-Ac, just as were the rats of Group III, but in addition they were bilaterally adrenalectomized (through two subcostal incisions under ether anaesthesia) at the time when they underwent unilateral nephrectomy.

In order to permit gradual adaptation to cold, the animals of Groups II, III and IV were first placed in a refrigerated room (in which the temperature varied between 0° and +3° C.) in cages containing five rats each. After three days, the fur of the back was clipped short and after three more days the fur of the whole body (except the limbs and the head) was clipped. The animals were again shorn once every week during the rest of the experiment.

COL-Ac was administered in the form of microcrystals, at the dose of 400 µg. in 0.2 ml. of water, subcutaneously, daily, in Groups III and IV. This treatment was indispensable for the maintenance of life only in the adrenalectomized rats of Group IV; but it was administered also to Group III, in order to verify whether even this small maintenance dose of a glucocorticoid could have modified the morphologic lesions induced by cold.

Throughout the experiment all the animals were maintained exclusively on Purina Fox Chow.

There was no mortality among the normal controls kept at room temperature, but in the course of the experiment five animals of Group II and two animals each in Groups III and IV succumbed. The survivors were killed with chloroform on the 56th day of the experiment. Immediately after autopsy, the kidneys and hearts of all rats were fixed in Susa solution for subsequent embedding in paraffin and staining with the periodic acid Schiff (PAS) technique.

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## RESULTS

Even before the termination of the experiment, it was noted that all the non-adrenalectomized rats (whether or not treated with COL-Ac) that had died spontaneously exhibited more or less pronounced signs of nephritis, nephrosclerosis, myocarditis and periarteritis nodosa of the heart. On the other hand, the two adrenalectomized rats that died showed no obvious cardiac or renal changes, and presumably succumbed only as a result of exposure to cold.

Histologic examination of the tissues taken from the survivors revealed pronounced and essentially similar changes in all the rats of Group II, and all but three of the rats of Group III, that is, in the non-adrenalectomized animals exposed to cold (whether or not they were treated with COL-Ac).

The renal changes in Groups II and III were characterized by: marked dilatation of the tubules with hydropic degeneration ("clear-cell nephrosis" type) of the tubular epithelia, enlargement of the glomeruli with proliferations of the epithelium of Bowman's capsule, exudation of a strongly PAS-positive, proteinaceous material into Bowman's spaces and hyalinization of the glomerular capillaries as well as of many of the afferent glomerular arterioles. Epithelial crescents were common and many of the convoluted tubules were obstructed by homogeneous hyalin casts. Dilatation of the tubules and hyperaemia of the glomeruli were also evident in the rats of Groups I and IV, but here, strictly pathologic changes, characteristic of nephritis or nephrosclerosis, were absent, except for an occasional hyalin cast such as may occur even in entirely untreated adult rats (Figs. 1 and 2). Careful inspection of the adrenal region at autopsy revealed remnants of cortical tissue only in two rats of Group IV and, interestingly, these were the only adrenalectomized animals in which signs of nephritis and nephrosclerosis were conspicuous.

The cardiac changes in Group II were characterized by: widespread periarteritis nodosa of the coronary arteries and occasional foci of hyalinization and inflammation in the myocardium. These same changes were also conspicuous in all but three of the non-adrenalectomized rats that received COL-Ac treatment during exposure to cold (Figs. 3 and 4). On the other hand, such lesions were completely absent in all the adrenalectomized animals exposed to cold except again for the two rats in which the operation was incomplete.

## DISCUSSION

It is evident from these observations that, after suitable "conditioning" (by unilateral nephrectomy and NaCl supplements), exposure to cold produces nephritis, nephrosclerosis, myocarditis and periarteritis nodosa of the cardiac

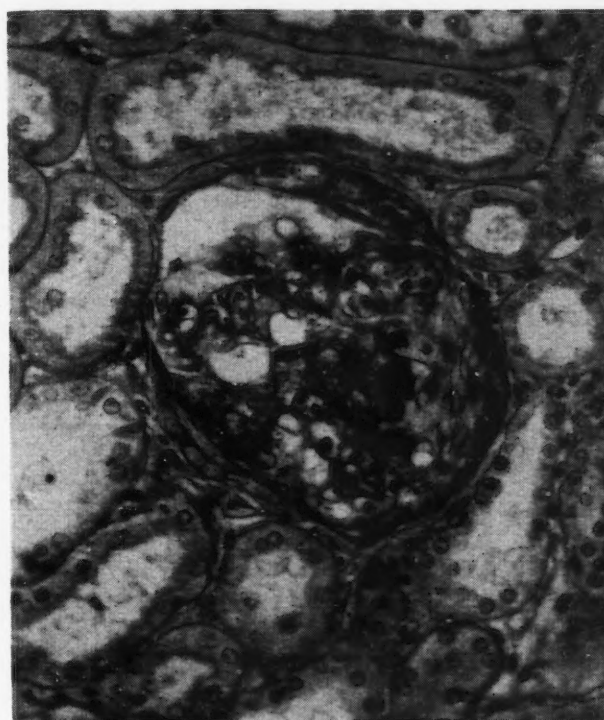


Fig. 1.—Enlargement of glomerulus with "crescent formation," deposition of PAS-positive material and capsular adhesions that developed during adaptation to cold in non-adrenalectomized rat of Group I ( $\times 200$ ).

vessels. The conditioning procedure itself did not elicit such changes and the small maintenance doses of COL-Ac failed to suppress them in the non-adrenalectomized animals kept in cold surroundings. On the other hand, complete adrenalectomy prevented the production by cold of the characteristic renal and cardiovascular



Fig. 2.—Similar changes in a non-adrenalectomized rat exposed to cold and treated with COL-Ac ( $\times 200$ ).

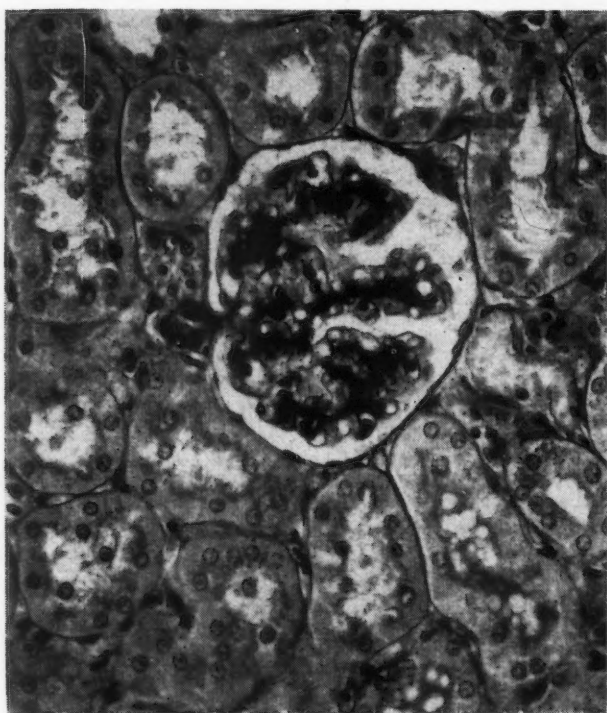


Fig. 3.—Intact glomerulus in an adrenalectomized rat exposed to cold and treated with COL-Ac ( $\times 200$ ).



Fig. 5.—Hyalinization and inflammatory infiltration of a papillary muscle in the heart of a rat of Group I ( $\times 120$ ).



Fig. 4.—Diffuse hyalinization and appearance of strongly PAS-positive material in the cardiac muscle fibres of a rat in Group I ( $\times 120$ ).

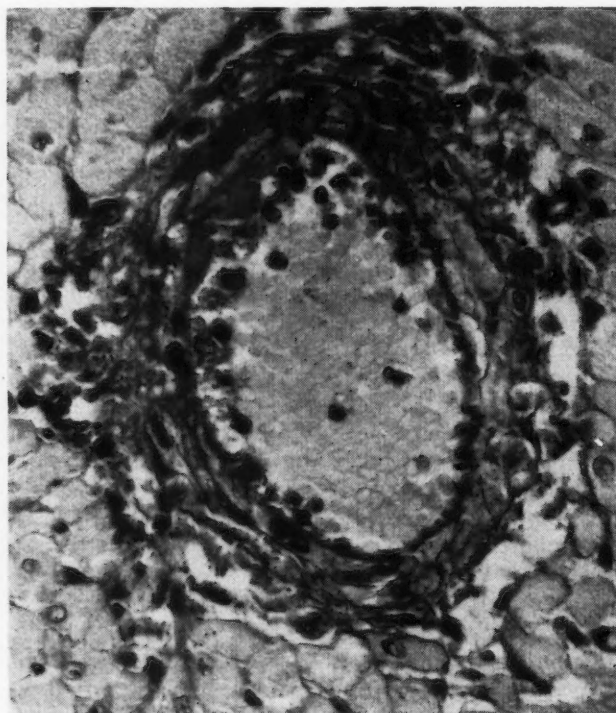


Fig. 6.—Beginning periarteritis nodosa with deposition of hyaline material underneath the endothelium of a cardiac arteriole in a rat of Group II ( $\times 350$ ).

lesions. The fact that the only exceptions to this were the two incompletely adrenalectomized rats furnishes additional evidence in support of the concept that the adrenals participate in the production of these lesions, presumably through the secretion of mineralocorticoids.

It remains to be seen, however, whether cold actually increases mineralocorticoid secretion or whether the salt-active hormones of the adrenal cortex merely condition the heart and kidney for the induction of morbid changes by cold. In the former case, the pathologic changes would



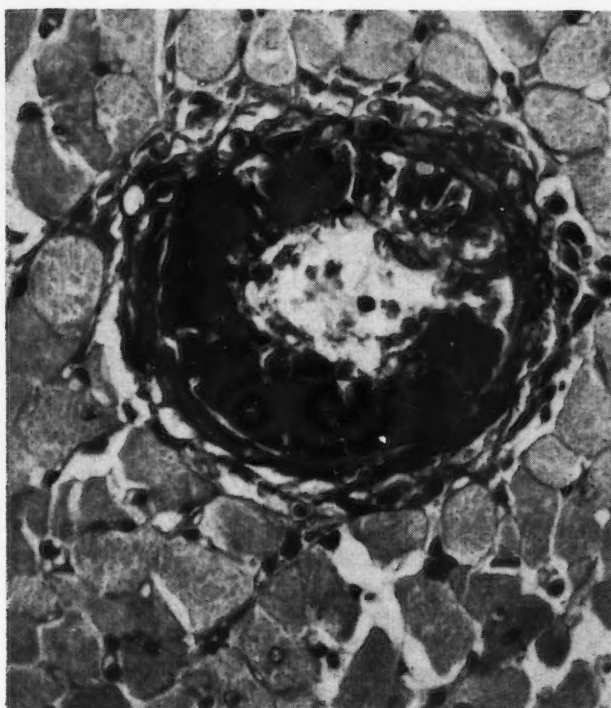


Fig. 7.—Intense subendothelial hyaline deposition in a cardiac arteriole of a rat of Group II ( $\times 350$ ).

be due to an absolute excess of mineralocorticoids; in the latter, to a relative excess, in the sense that normal amounts become sufficient to produce signs of overdosage, because adaptation to cold sensitizes the receptive tissues. The evidence available to us at present does not

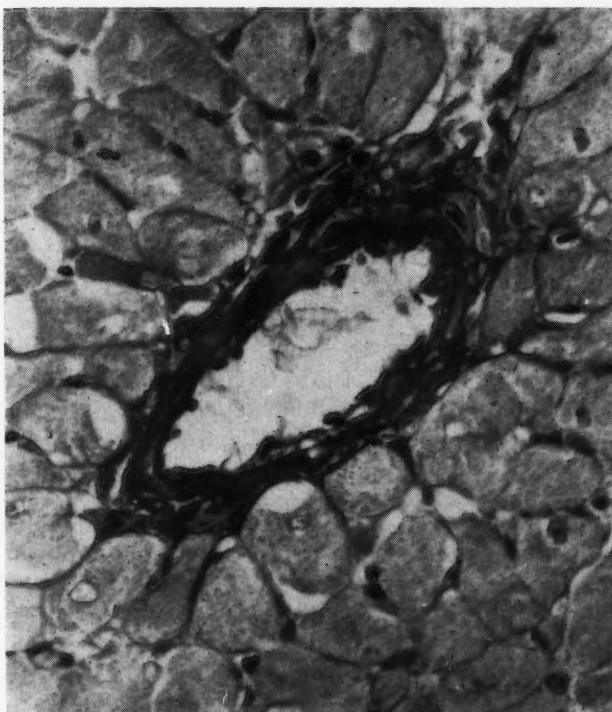


Fig. 8.—Cardiac vessel (comparable in size to those shown in Figs. 6 and 7) from a rat of Group III in which cardiac periarteritis nodosa was prevented by adrenalectomy ( $\times 350$ ).

make it possible to distinguish between these two possibilities, but in either case it is clear that the adrenals have a decisive influence in the production of pathologic organ lesions during adaptation to cold.

#### SUMMARY

In rats "conditioned" (by unilateral nephrectomy and NaCl supplements) for the production of mineralocorticoid overdosage, prolonged exposure to cold produces nephritis, nephrosclerosis, myocarditis and periarteritis nodosa of the cardiac vessels. These changes do not occur in the absence of the adrenals. It is concluded that hormones normally secreted by adrenal cells have a decisive influence on the production of these morbid changes during adaptation to cold.

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### PERPHENAZINE (TRILAFON) THERAPY—A PILOT STUDY\*

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#### INTRODUCTION

PERPHENAZINE (Trilafon) came to us recommended as a potent tranquillizing agent. Reports indicated that blood pressure effects had been noticeably absent and other side effects such as parkinsonian symptoms had cleared with reduced dosage. At this hospital chlorpromazine has proven the most generally useful of the new drugs used in psychiatry, but we still have many patients who do not respond to chlorpromazine. A limited trial of perphenazine was undertaken to assess its usefulness in the mental hospital setting and to compare it with chlorpromazine.

#### SELECTION OF PATIENTS

Twenty-eight patients were selected for treatment. All but one of these were long-stay

\*From the Brandon Hospital for Mental Diseases, Brandon, Manitoba.

patients who had proved resistant to other forms of therapy. Nineteen had previously received chlorpromazine. Their response to chlorpromazine had been negative or resulted in only temporary improvement.

#### TREATMENT

Patients were started on 8 mg. perphenazine a day and this was increased in some cases to as much as 72 mg. per day, but the average treatment dose was 32 mg. per day. Length of treatment ranged from twenty days to seven months with an average of over 100 days. Tablets of 4 mg., 8 mg., and 16 mg. were used. The 8-mg. tablets seemed to be the most practical for use in the hospital setting.

#### GENERAL RESULTS

Seven patients were much improved. In five of these there was every indication that this improvement was directly associated with the medication. In the other two cases the association was not so direct, but the fact remains that they have shown a marked improvement and have left the hospital. Five others showed improvement while 16 appeared to be unimproved or at best only slightly improved.

On the whole these do not seem to be very encouraging results, but when the type of patient selected is kept in mind they present a different picture. Take, for example, patient A.P., who had been in hospital since 1945, showing little or no improvement from insulin, electroconvulsive therapy, or drug therapy including Pacatal and chlorpromazine. At the start of her perphenazine therapy she required single-room care most of the time because of her irritability and combativeness. Today she has single parole, is a very good worker, and seems to enjoy her work. She has been on a maintenance dose of 16 mg. of perphenazine per day for six months and she is still improving.

#### SIDE EFFECTS

Over 50% of those treated (15 patients) showed no evidence of any side effects. Eight exhibited tremor and other parkinsonian symptoms, while five exhibited a drowsiness sometimes approaching a stupor. All these side effects cleared with a reduction in dosage or after treatment was discontinued.

#### GENERAL COMMENTS

We have not sufficient evidence here to indicate that perphenazine (Trilafon) can replace chlorpromazine, but we have indications that it can help a significant number of patients resistant to chlorpromazine therapy and bring some of them close to if not to the level of recovery (three of our group have been paroled).

Improvement is rather slow in developing on oral medication. From two to three weeks passed before definite evidence of improvement was available in three of the much improved cases. Some signs of improvement had appeared earlier but a sceptical staff would not allow these as evidence of real improvement because all these patients show spontaneous changes in behaviour. It was not until improvement had passed well beyond anything previously experienced that agreement as to actual improvement was reached.

Side effects did not seriously interfere with therapy.

It would appear that doses up to 48 mg. a day could be given routinely. Side effects will develop in almost half of the patients receiving this dosage, but if the latter is reduced to a maintenance dose of 16 mg. a day most of these will clear and in most cases the beneficial mental effects will be retained. As with other drugs of this type, however, dosage must be individually adjusted—some of our patients required 72 mg. per day whereas others had a good result on doses no higher than 16 mg a day.

#### CONCLUSION

Perphenazine (Trilafon) should prove to be a useful drug as a supplement to chlorpromazine in the mental hospital setting.

We wish to thank Schering Corporation Limited, Montreal, for their generous supplies of Trilafon for use in this study, and also the staff of the Brandon Hospital for Mental Diseases, without whose assistance this investigation could not have been carried out.

### AN INVESTIGATION OF ABNORMAL UTERINE BLEEDING\*

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ABNORMAL uterine bleeding is a very common gynaecological condition. It should never be ignored. A procedure which is simple, yet efficient, is much more likely to be employed than one which is complicated and difficult. The procedure used in this investigation is simple

\*Aided by a grant from The Ontario Cancer Treatment and Research Foundation.

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and reliable. While the series of patients is not as large as some others<sup>1</sup> which have been reported, it is felt that the methods of investigation have been tested thoroughly and the follow-up has been adequate in all cases.

The purpose of this study was to develop a simple yet reliable procedure for the investigation of women with abnormal uterine bleeding, by means of which uterine malignancy could be proved or ruled out.

The methods of investigation consisted of careful inspection of the cervix through a vaginal speculum, exfoliative cytology and the obtaining of a tissue biopsy whenever indicated. The tissue biopsy was a biopsy of cervix or/and an endometrial biopsy by Novak curette. For a study of exfoliative cytology by the Papanicolaou technique, smears were prepared of vaginal secretions and of gentle scrapings from the cervix; for an adequate trial period, whenever indicated, smears of endometrial fluid aspirated by Carey cannula were examined. Later the examination of endometrial fluid was abandoned because it contributed little to the investigation. For approximately the last 400 cases, smears of material collected directly from the cervix were used almost solely for exfoliative cytology, these being found most satisfactory. For the first 1798 cases duplicate smears of all material for exfoliative cytology were made, one being stained with Papanicolaou stain E A 50 and O G 6, the other with hæmatoxylin and eosin. Subsequently H and E stain was used solely.

To the time of writing, 5220 smears obtained from 2243 patients have been examined. All smears have been examined and interpreted by one pathologist (J.H.F.); thus the personal factor in interpretation has been minimized. In a large number of women at the Ontario Hospital, London, Ontario, exfoliative cytological screening was carried out as part of a routine gynaecological examination. However, follow-up information on these patients is not available and they have been excluded from this report. Of the total of 2243 patients examined, 1178 with satisfactory follow-up are suitable for analysis. In summary the results are as follows:

Patients examined.....	1178
Positive smears.....	99
Patients biopsied.....	523
Cervical carcinoma.....	106
Endometrial carcinoma.....	39
False positive smears.....	11
endometrial carcinoma.....	1
cervical carcinoma.....	10
False negative smears.....	47
endometrial carcinoma.....	26
cervical carcinoma.....	21
False negative biopsy of cervix.....	2
False negative biopsy of endometrium.....	2

Occasionally the term "suspicious" was used in reporting smears. This meant that there was insufficient evidence for a positive smear diagnosis but the findings were sufficiently atypical

to warrant further investigation. Suspicious smears were recorded as negative.

Errors in diagnosis occurred chiefly in the early days of the investigation. As the experience of the cytologist increased, diagnostic accuracy improved. The incidence of false negative smears was much higher in endometrial than in cervical cancer. Some of the false negative smears in cervical cancer were due to previous cervical conization or biopsy in cases referred here later for further investigation. Adenocarcinoma of the cervix is apt to give false negative smears because the cancer cells apparently do not desquamate as readily as in squamous cell carcinoma. A source of false positive smears occurred in irradiated cervical cancer. In some of these cases benign irradiated cells were interpreted incorrectly as cancer cells.

#### SUMMARY AND CONCLUSIONS

1. A simple diagnostic investigation which requires neither hospitalization nor anaesthesia has been outlined for women who have abnormal uterine bleeding or who wish to be examined for the possibility of uterine cancer. Briefly the procedure consists of careful inspection of the cervix with vaginal speculum, exfoliative cytology and examination of a biopsy, either cervical or endometrial, when indicated.

2. The results in 1178 patients in whom this procedure was followed and in whom there was adequate follow-up information, have been analyzed.

3. Exfoliative cytology is an important adjunct in the detection or exclusion of cervical cancer. For the detection of cervical cancer, faith in it as a diagnostic aid is amply justified. In the detection of endometrial cancer, it gives too many false negative smears, and therefore is unreliable.

4. Exfoliative cytology does not replace the adequate biopsy which must remain the most important single investigative and confirmatory procedure.

5. It is our opinion that cells and secretions scraped directly from the cervix allow a more accurate and less complicated cytological test than vaginal smears.

6. In our experience smears stained with hæmatoxylin and eosin were equally as reliable for the diagnosis of cancer as those stained with the Papanicolaou stain.

7. Some reasons for false reports have been given.

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## MEDICAL MANPOWER

From time to time voices are raised to inquire about the state of medical manpower in Canada. Are there too many physicians in the country? Or too few? What is meant by "too many" or "too few"? Too few for what? How many will we need in ten years? In twenty years? These are enormously difficult questions to answer and if the manpower problem is probed even further and the needs are analyzed in terms of different categories of physician, what was difficult becomes almost impossible. For who can say what the next decade in medical research will bring forth? The venereologist and the tuberculosis physician have both seen their spheres of action contract unexpectedly; an effective cancer chemotherapy could do the same for the general surgeon, and many other unknowns could seriously upset the delicate balance. And it is no longer sufficient to speak in general of an underdoctored area, for doctors are not as adaptable as they were. Inhabitants of a province with a surplus of pædiatricians and radiologists and a deficiency of obstetricians would not be happy to know that its total of physicians was just right for the population needs. It is true that in field conditions in wartime radiologists have been known to give anæsthetics with a bottle and mask, and a neurosurgical team has been seen amputating limbs quite happily, but each decade sees the advent of more and more super-specialists who, in case of unemployment, would find it increasingly difficult to switch over to another branch of medicine.

In spite of this, and in the face of gloomy prophecies of failure, a departmental committee appointed in February 1955 to examine the state

of medical manpower in the United Kingdom have succeeded in bringing in a report<sup>1</sup> which stamps them as courageous if not positively clairvoyant. The committee, under the chairmanship of Sir Henry Willink, was asked to estimate on a long-term basis the number of medical practitioners likely to be engaged in all branches of the profession in the future and the consequent intake of medical students required. The main stimulus to the appointment of the committee was the widely expressed fear that the profession was becoming overcrowded in Britain.

The committee's report states that this fear is groundless. There are indeed still gaps to be filled. Many general practitioners are carrying more patients on their lists than the stated ideal of 2500 for urban and 2000 for rural areas. (If these figures seem absurd, it must be remembered that the British general practitioner renders a much more circumscribed range of services than his Canadian counterpart.) There are unfilled junior posts in hospitals (over 700 in 1955) and deficiencies in some specialties. It is hoped that a reduction within the next few years in the Armed Forces will release enough physicians to fill all these gaps in conjunction with the current output from medical schools. It is suggested, however, that by 1961 a medical school output of 90% of the present figure will be adequate, and that therefore the medical schools of Britain should cut their intake by 10% as soon as possible. They are of course under no compulsion to do so, though a cut in government grants to them could always be used as a method of persuasion.

A few interesting sidelights emerge from the report. Thus the number of unemployed doctors in Britain is described as very small, a finding at variance with the statements of certain "angry young men" who complain to the editor of the *British Medical Journal* from time to time. At present 400 doctors emigrate from Britain annually (a figure thought likely to fall in future years) while 200 a year settle in Britain, mostly from Ireland and the Commonwealth. The committee consider that hospital and specialist services will continue to expand, while overseas opportunities for British physicians diminish.

What do all these figures mean? They do not mean that if all these predictions are correct and action based on them is taken the British population will have an ideal medical service—even



supposing we could define an ideal service. They mean, as British editorial writers have been quick to emphasize, that with these numbers of physicians the British public will get precisely the services that its government thinks it should have and can afford to pay for. Used as a very rough guide by the profession and the medical schools, they could be helpful; used by government to restrict supply and demand, they could be disastrous.

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### Editorial Comments

#### RECURRENT OTITIS MEDIA IN CHILDREN

Some months ago, the Sections of Otology and General Practice of the Royal Society of Medicine met together to discuss this important and troublesome subject, from the aspect of epidemiology and changing clinical course and treatment over a considerable period of time. An attempt was made to obtain a critical objective re-assessment of the condition from general practitioner and specialist viewpoints. Because of the wide incidence of this disease and the complications that may ensue, it is considered advisable to give wider dissemination to some of the points that arose during the discussion.

Dr. I. Friedmann, pathologist at the Institute of Laryngology and Otology, discussed the bacteriology of many hundreds of cases of otitis media. He showed that the incidence of the predominant organism is not changing; we are not more troubled with the penicillin-resistant staphylococcus now than we were some years ago. Also pathological examination does not indicate a change in the pathological process of otitis media. In experimentally produced otitis media, Friedmann showed that results were good when antibiotic therapy was commenced by the seventh day of the disease; after that time many chronic infections resulted. In the discussion of antibiotic therapy, the time-honoured question was raised whether the improvement in treatment of otitis media was entirely due to the advent of antibiotics or if, in addition, the virulence of the organism had changed. As in the past, a satisfactory answer could not be obtained.

The clinical aspect of otitis media was presented in a comprehensive manner by Mr. Lionel Taylor, a well-known otologist. His paper suggested several causes for otitis media and free discussion ensued on each point.

1. *Dental eruptions.*—It has not been established that the cutting of teeth plays an important part in inflamed ears.

2. *Enlarged adenoids.*—Mr. Taylor discussed the physical factor of blockage of the Eustachian tube, and recommended adenoidectomy when clearly indicated for the benefit of this aspect of the disease. Associated tonsillectomy may or may not be done, depending on the pathology in the tonsils; tonsils themselves have no bearing on ear infections. In the discussion of this point, it was shown that some ear infections were due to adenoviruses which persisted in the adenoid tissue for long periods of time, causing further hypertrophic changes. The general opinion was that an *adequately* performed adenoidectomy (and this was stressed) was usually of benefit in controlling recurrent infections.

3. *Perforations.*—The presence of perforations of the tympanic membrane predisposes to recurrent infection after swimming or syringing of the ears for removal of cerumen. It was agreed that there was a greater tendency to persistent perforations after spontaneous rupture of the drum than after myringotomy. A brisk argument on the necessity of myringotomy produced the points that resolution is more rapid and relief of pain more prompt when the products of infection are released from the middle ear by an incision in the drum. It also presents an opportunity to obtain material for culture and sensitivity testing. Surveys have been carried out to show a waning incidence of myringotomies, but the same surveys did not consider if an increase in hearing disability in later life was concomitant with the decrease in surgical procedures. It was drawn to the attention of the members that sometimes myringotomy is necessary two or three weeks after the acute onset to rid the middle ear of residual products of infection, often in the form of gelatinous exudate. It was also mentioned that too early myringotomy, before the formation of exudate, seldom was beneficial either in relieving pain or decreasing infection.

4. *Latent infections.*—This discussion pertained to the serious complications of otitis media, namely, meningitis, lateral sinus thrombosis, brain abscess, labyrinthitis with loss of hearing, which may suddenly flare up in an apparently quiescent ear because of inadequate antibiotic therapy, "inadequate" from the standpoints of improper selection or insufficient dosage. It was considered that the optimum coverage was a combination of penicillin and sulfonamide in full dosages and might even give beneficial results in the presence of staphylococci shown, *in vitro*, to be penicillin-resistant.

5. *Idiopathic.*—A certain number of cases present no predisposing pathological conditions and usually the symptoms disappear about age 14 years.

From these presentations and discussions the following points may be stressed: (1) Bacteri-

ology and pathology of otitis media is remaining constant over the years. (2) Early antibiotic therapy is most beneficial in otitis media, the best all-purpose coverage being penicillin and sulfonamide. This must be adequate in dosage and duration of administration to prevent complications. (3) Myringotomy is still a useful procedure in many cases. (4) Properly performed adenoidectomy in indicated cases helps prevent further recurrences. To these we would add one further point: each patient should be kept under observation until the hearing has returned to the pre-infective level. By the observance of the foregoing points, the treatment of recurrent otitis media in children will be on a sound basis.

GORDON H. FRANCIS

#### HYPERTENSION AND EMOTIONAL STRAIN

There is probably no human ailment whose etiology has been claimed by as many medical specialties as has hypertension. During the "Goldblatt era" there was occasionally a great deal of difficulty in preventing the surgical removal of mildly diseased but probably essentially innocent kidneys. The endocrinologist has also had his fling with renin, hypertensinogen, hypertensin, serotonin, antiserotonin, the adrenal medulla and cortex—and *stress*. The neurologists, for a short time, popularized their theories of the importance of the hypothalamus and the autonomic nervous system—and the neurosurgeons performed many sympathectomies. At present, the problem is in the hands of the departments of pharmacology and materia medica, with reserpine (nasal obstruction, abdominal cramps, nightmares and depressive psychoses); ganglionic blocking agents (gastrointestinal atony, abdominal distension, constipation); hydralazine (lupus erythematosus-like syndrome); and countless others. This phase is most probably destined to go the way of the other antihypertensive therapies, although it has been of some value in indicating that there is more than one site of causation of essential hypertension.

There is one specialty, however—psychiatry—that has repeatedly assumed the status of a vested interest in the matter of hypertension, and has remained in an undisturbed position as each doctrinal phase has passed. To this specialty, the cerebral cortex has been primarily and intrinsically in the position of responsibility, even during the urological, the endocrinological, and, to a lesser extent, the pharmacological phases. And, with the decline in importance of these theories, the psychiatrist bids fair to sit in solitary grandeur on the etiological throne, if only by default. This is, of course, the result of the enlistment by the psychiatrist of all the available biochemical and physiological tech-

niques to fortify his psychologic concepts. This is described as "the psychosomatic approach". Recent "psychological" studies along these lines have involved measurements of peripheral vascular resistance, cardiac output, stroke volume, heart rate, hand temperature, psychogalvanic skin response (*sic*), muscle potential, inspiratory index and respiratory rate, during induced pain, fear and anger in hypertensive and non-hypertensive subjects. One was surprised to learn that "different psychologic intensities of anger tend to be associated with different physiological responses, though the differences are not statistically significant". It appeared important to note, however, that, during induced pain, fear and anger, "the variance of the blood-pressure responses of the hypertensives exceeded that of the non-hypertensives". In other words, extensive physiologic investigation proves conclusively that a hypertensive responds to pain, fear and anger by—of all things—hypertension!

Clearly, we have not yet heard the last word on this fascinating subject.

S. J. SHANE

#### NICOTINIC ACID AND HYPERCHOLESTEROLÆMIA

Arteriosclerosis plays so prominent a role in today's pathology that it is not surprising that a great deal of research is directed toward determining its cause and its treatment. Serum lipids (cholesterol and beta lipoproteins) undoubtedly have some significance in its pathogenesis although several other factors must be at play. Evidence for the role of lipids has been often given and depends mainly upon the observations that populations consuming much fat show the effects of atherosclerosis to a greater extent than those on a low fat diet. Some species made hypercholesterolaemic develop relatively more atherosclerosis than their normal counterparts. Against this hypothesis is the observation that although elevated lipid levels precede coronary disease, lipid levels alone do not predict accurately the further development of such attacks.<sup>6</sup>

Although the role of lipids is not clear, it appears desirable to lower their level if it is elevated by modifying the most modifiable factor. For this reason, much interest has developed in methods of lowering serum cholesterol level. These include (a) dietary measures such as decreasing the total caloric intake and the fat intake in general and particularly the amounts of animal fat and saturated fats, (b) decreasing absorption of fat from the bowel, (c) altering metabolic processes by administering hormones, vitamins or ultraviolet irradiation. These methods suffer from one or more of the following defects: (a) they are relatively in-



effective, (b) they are impractical because they grossly interfere with established dietary habits amongst other reasons, (c) they have undesirable side reactions.

It is thus of great interest to note that a group of Saskatchewan scientists have introduced an effective hypocholesterolaemic agent which has none of the disadvantages listed and which seems to surpass other treatments so far developed.<sup>3-8</sup> When nicotinic acid is administered in adequate dosages to hypercholesterolaemic rabbits, there is a significant and marked decline in their cholesterol levels.<sup>3</sup> Hypercholesterolaemic human subjects react similarly.<sup>5</sup> The decrease is usually greater when the initial levels are high. Nicotinamide is ineffective. When nicotinic acid is added to an atherogenic diet for rabbits, there is marked inhibition of the expected atherosclerosis.<sup>3</sup> Nicotinic acid produces a significant but very slight increase in basal metabolic rate.<sup>4</sup> The effect on the cholesterol level is similar for normal controls,<sup>4, 5</sup> patients in a general hospital,<sup>5</sup> schizophrenic patients,<sup>7</sup> and patients in a mental hospital.<sup>8</sup>

Confirmation of these studies has come rather quickly. Marked decrease in cholesterol and in beta lipoproteins was observed in 9 out of 13 patients treated 12 weeks or longer.<sup>9</sup> A more recent study on 24 patients gave similar results.<sup>10, 11</sup> The authors conclude that "the results suggest that the use of large doses of niacin may prove to be the most practical method introduced to date for reduction of elevated

plasma cholesterol levels to normal without dietary restriction". Finally from a careful two-year study,<sup>1</sup> it was concluded that "the use of nicotinic acid in large doses to reduce increased concentrations of blood lipids appears effective, practical, and probably free from serious harmful effects".

One side effect is the cutaneous vasodilatation and pruritus that occurs when medication is started. This is usually overcome in a few days. However, recently a method of preparing niacin has been developed which will overcome this inconvenience. Nicotinic acid will then be practically free from side reactions.

There is little doubt that these findings will open up new channels for biochemical investigations and provide hope that by decreasing cholesterol and beta lipoprotein levels with nicotinic acid, the pathological sequelae of hypercholesterolaemia may be mitigated or prevented.

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### IT'S LATER THAN YOU THINK

Although the enrolment in the CANADIAN MEDICAL RETIREMENT SAVINGS PLAN has been increasing steadily, a large number of potential participants have not yet applied. To obtain tax deferment on your retirement savings for the year 1957, it is essential that you submit a completed application before December 31st. Deposits in your retirement savings account at The Bank of Montreal, applicable to the taxation year 1957, may be made until February 9, 1958.

C.M.R.S.P. is an outstandingly good plan which brings to you the advantages of group savings and the administrative resources of The National Life Assurance Company of Canada, The Royal Trust Company, and The Bank of Montreal.

To take advantage of this excellent opportunity to save for your retirement and to save current tax, you must take the first step. Complete the application card which reached you with the C.M.R.S.P. brochure in late September and submit it without delay to the Canadian Medical Retirement Savings Plan, 150 St. George Street, Toronto 5.

## Medical News in brief

### TREATMENT OF PEMPHIGUS WITH STEROIDS

Steroid therapy is the treatment of choice for pemphigus, according to Costello of New York and his colleagues (*J. A. M. A.*, 165: 1249, 1957). These authors have treated 270 patients in the period 1911 to 1951, and another 52 patients in the period 1951 to 1955. The latter series received corticosteroids in the form of ACTH administered intravenously, repository ACTH intramuscularly, or cortisone, hydrocortisone or prednisone given orally. They mention a series of equivalents; for instance, daily dosage of cortisone varied from a minimum below 50 mg. to a maximum above 500 mg.; the corresponding limits for prednisone were below 10 mg. and above 100 mg. The former high mortality rate of pemphigus (above 90%) has been reduced to about 33%. A few patients have been free of signs and symptoms for one, two or more years without further steroid treatment, while others have needed daily maintenance doses. Steroids have been of most value in the treatment of pemphigus vulgaris, of less value in pemphigus erythematosus and of little permanent benefit in pemphigus foliaceus. The cause of the disease is unknown, and the reason for its high incidence among adult Jews is also unknown.

### MECHANISM OF ACTION OF TOLBUTAMIDE

The mechanism of the hypoglycaemic sulfonamides, carbutamide and tolbutamide, is still obscure. Caron and Corbo (*J. Clin. Invest.*, 36: 1546, 1957), studying the combined effects of tolbutamide and insulin on completely depancreatized dogs, find that tolbutamide potentiates the action of exogenous insulin in the absence of all pancreatic tissue. The drug affects both intensity and duration of insulin activity; prolonging the duration appears to be the more important clinical effect. In addition, of course, tolbutamide may partly act by stimulating beta cells.

### SPINAL DEFECTS AND FLUORIDE

In 1942 some British observers reported that osteochondritis of the spine, of the type described by Scheuermann, was fairly common in children living in Oxfordshire villages where the level of fluoride in the water was 0.3-1.2 parts per million. The worst cases were in four children with a history of defective nutrition in early years. At the time it was thought that fluoride might play a causal role in these spinal changes. A further survey in the east of England seems to establish that this is not true. Eley and his colleagues radiographed the dorsal and lumbodorsal spines of boys aged 11-14 in high-fluoride and low-fluoride areas, selecting also special sub-groups of boys with possible mal-

nutrition. No evidence was obtained from this survey that exposure to fluoride in amounts of 1.5-5.8 p.p.m. in drinking water, or for that matter malnutrition, was associated with spinal defects. —Eley *et al.*, *Lancet*, 2: 712, 1957.

### ATARACTICS AND CONVULSIONS

Fazekas and his colleagues from Washington, D.C. (*J. A. M. A.*, 165: 1249, 1957), warn that in a small proportion of cases (under 10%) the administration of phenothiazine derivatives, such as chlorpromazine and promazine, to psychotic patients may induce convulsions. These drugs in relatively large doses appear to have an epileptogenic tendency in individuals susceptible to seizures. Among patients being treated for alcohol or barbiturate addictions withdrawal convulsions during abstinence tended to obscure the picture. It is likely that individuals susceptible to convulsions should be given anticonvulsant medication if they are to receive these tranquilizers.

### EXPECTORANTS AND SPUTUM VISCOSITY

Many generations of practitioners have prescribed such expectorants as ammonium salts, ipecacuanha and potassium iodide in the belief that these expectorants made the sputum less viscid. Forbes and Wise (*Lancet*, 2: 767, 1957) studied sputum viscosity before and after the administration of these expectorants and also before and after inhalation of steam, 5% carbon dioxide and oxygen, an aerosol detergent, and aerosol proteolytic enzymes. No support could be found for the belief that the currently available expectorants when administered in the usual intermittent manner effectively altered sputum viscosity, although such lowering has been demonstrated elsewhere *in vitro*. The other treatments were no more successful. The authors say, "It is odd that medicaments whose therapeutic value is supported by so little objective evidence continue to be so popular with both doctors and patients."

### BASAL CELL CARCINOMA METASTATIC FROM SKIN TO LUNGS

Although this is very rare, basal cell carcinoma can metastasize, especially if the primary tumour has existed for many years with considerable enlargement and ulceration. Huntington and Levan (*A.M.A. Arch. Dermat.*, 75: 676, 1957) report a basal cell carcinoma, of 23 years' duration, on the nose of a 66-year-old white man who at autopsy had numerous 2-cm. nodular masses scattered throughout the upper and lower lobes of the right lung. Microscopic examination revealed an adenocystic type of basal cell from the nose and in the lung. There were no squamous elements.



## REVIEW ARTICLE

### SOME BASIC FEATURES OF OPEN-HEART SURGERY USING THE BUBBLE OXYGENATOR

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IN MARCH 1954, at the University of Minnesota Hospitals, the clinical use of extracorporeal circulation became a reality and with it a new concept of cardiac surgery began. For the first time it was possible to open the diseased heart without fear of uncontrollable ventricular fibrillation and without being harassed by limitation of operating time.

Since then the basic principles and techniques of extracorporeal circulation have become fairly well standardized so that, during cardiac bypass, blood from the superior and inferior vena cava is diverted through plastic tubing before it reaches the right atrium and is pumped to an artificial lung (oxygenator). Blood, as it passes through the oxygenator, picks up oxygen and carbon dioxide is blown off. It is then pumped into the subclavian or femoral artery to complete the circuit. While the experiences reported here pertain chiefly to the bubble-type oxygenator, there are actually three basic types in clinical use.

The first is the bubble oxygenator designed by DeWall and Lillehei of Minneapolis.<sup>1</sup> The apparatus consists of a metre-long vertical plastic tube into the bottom of which venous blood and oxygen are bubbled while fully oxygenated blood emerges at the top. The blood then passes into an inclined siliconized tube which breaks the bubbles before the blood is returned to the patient via a systemic artery.

The second is the screen oxygenator, originated by Gibbon of Philadelphia,<sup>2</sup> which consists of a parallel series of fine meshed vertical screens housed in a plastic case. Venous blood, while flowing down the meshes of the screen in a thin film, is exposed to pure oxygen. The oxygenated blood then passes into a reservoir and is returned to the patient as required.

The third basic type is the membrane oxygenator devised originally by Kolff of Cleveland and modified by Clewes.<sup>3</sup> It consists of a series of rubber units placed on top of each other. The unit is about three feet by one foot by one-quarter inch, and sandwiched between each are two longitudinal semipermeable plastic membranes through which flows a thin layer of venous blood. Oxygen circulates in a layer outside the two membranes and gradually diffuses through to mix with the venous blood while

carbon dioxide diffuses outward. Oxygenated blood from the units is collected in a small reservoir and pumped to the patient's subclavian artery.

The advent of pump-oxygenators has made corrective surgery possible for many congenital and acquired cardiac lesions previously considered inoperable. Using open heart surgery, corrective techniques are now well founded for ventricular septal defect, auricular septal defect, atrioventricular canal, tetralogy of Fallot and pulmonary stenosis, either valvular or infundibular. Although fewer patients have been operated upon, corrective techniques are well founded in total anomalous pulmonary venous drainage, mitral regurgitation, aortic stenosis, aortic-pulmonary window, ruptured sinus of Valsalva, and fusiform aneurysms of the aorta ranging from the coronary ostia to the left subclavian artery. However, there are many lesions such as complete transposition of the great vessels, truncus arteriosus and common ventricle for which satisfactory corrective procedures have yet to be developed.

In University Hospital, Minneapolis, over 325 intracardiac defects have been repaired using the bubble oxygenator. Over-all survival has remained above 70%, and in favourable groups the results are steadily improving. For example, 94.3% of 102 patients operated upon over one year of age with a ventricular septal defect and a pulmonary artery pressure under 50 mm. Hg have survived, and in 18 patients with auricular septal defects of the ostium secundum type the operative mortality has been zero.

#### INDUCED CARDIAC ARREST

Techniques in intracardiac surgery are hampered by blood in the operating field. When the right ventricle is opened, the field is often obscured by blood from the coronary sinus and from bronchial collateral circulation passing retrograde from the pulmonary artery or flowing into the left heart via the pulmonary veins and across the ventricular or auricular septal defect. Also, blood may obscure the field by spilling across the aortic valve which, even though normal, often exhibits varying degrees of incompetency when the supporting myocardium of the right ventricle is opened. Furthermore, in open heart surgery, persistent activity of the myocardium renders accurate surgical repair of many congenital and acquired defects both difficult and occasionally incomplete.

In 1955,<sup>4</sup> for the first time, chemically induced cardiac arrest was added to open heart surgery, the myocardium was stopped, its metabolism lowered, the surgical field dried, and danger of air embolism greatly reduced. Several arresting drugs were used experimentally but only two, acetylcholine and potassium citrate, seemed to have the properties of an ideal cardioplegic agent, namely, the rapid induction of complete

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cardiac standstill, rapid restoration of sinus rhythm with re-perfusion of the coronary arteries and absence of systemic toxicity. Lam<sup>4</sup> has favoured the use of acetylcholine to induce cardiac arrest while Effler,<sup>5</sup> Lillehei<sup>6</sup> and others have chiefly used potassium citrate.

Sidney Ringer<sup>7</sup> in 1883 first recorded depression of the myocardium when potassium chloride was added to the perfusing fluid of an isolated heart. The pathophysiology is best illustrated if one takes a single cell as an example. The outside of the cell membrane contains positive electrical charges, and the inside, negative charges which result in the cell having a negative electrical potential of about 90 millivolts. When a cell contracts, potassium passes outwards but when the extracellular potassium concentration is increased, as in cardiac arrest, the positive potassium ions within the cell cannot pass outward against the high concentration. The resulting increase of positive charges within the cell reduces the negative electrical potential of that cell and it cannot respond to further stimulation until the potassium concentration in the extracellular fluid is reduced. It is then possible for potassium cations to pass out of the cell, thus restoring the negative electrical potential.

During arrest, although the heart is functionally inactive, its metabolism continues and, as Rhodes has shown, oxygen consumption of the potassium-arrested heart is reduced only to 50% of that in the beating non-working heart.

Induced cardiac arrest with acetylcholine does not act by reducing the negative electrical potential of the myocardium but functions by preventing neural impulses bridging the myoneural junction. Normally the myocardium contracts after acetylcholine has been hydrolyzed by cholinesterase, but when the enzyme system is overwhelmed it cannot remove acetylcholine, and impulses at the myoneural junction are ineffective.

Cardioplegic agents are administered by rapid injection through an 18- or 19-gauge needle into the ascending aorta just proximal to an aortic clamp placed one inch distal to the ostia of the coronary arteries. Action of the myocardium ceases quickly and remains dormant until the aortic clamp is removed and oxygenated blood perfusing the coronary arteries washes out the paralyzing drug.

Acetylcholine, injected at a concentration of 10 mg. per kg. of body weight, produces cardiac arrest but a single contraction may occur each time the myocardium is touched. In potassium asystole the higher the concentration used or the greater the duration of arrest, the longer it takes to resuscitate the heart once coronary perfusion begins. At present, a 2½% solution (25 mg. per c.c.) is used and is prepared by expanding a 25% solution of potassium citrate with the patient's own arterial blood.<sup>8</sup> The upper limit of safety has not been established but a solution of less than 1 mg. per c.c. (0.1%

solution) will not produce cardiac arrest. When injected rapidly, the average amount of 2½% potassium citrate solution required to produce asystole in adults is 25-35 c.c., while children require only 10-25 c.c.

In patients with aortic valvular disease or ruptured aneurysm of the sinus of Valsalva, it is often difficult to produce elective cardiac arrest because the drug regurgitates into one or other ventricle instead of passing through the coronary arteries.

The duration of elective cardiac arrest reported from several centres varies from 10 to 40 minutes; the longest arrest of which the author is aware was 82 minutes, which was followed by uncomplicated resuscitation. As a rule, the longer the period of induced arrest, the more frequent are arrhythmias and the more difficult it is to resuscitate the heart in the post-potassium phase. It seems advisable for the maximum period of induced arrest not to exceed 30 minutes. In some centres induced cardiac arrest is used routinely in all cases of intracardiac surgery. In others, such as the University of Minnesota Hospitals in Minneapolis, potassium asystole is used only to facilitate difficult exposures and thus expedite a durable repair in the various types of septal defects. In Minneapolis the increased incidence of persisting atrioventricular dissociation associated with potassium arrest has deterred routine use of the drug in intracardiac surgery.

#### SURGICAL COMPLICATIONS

Two serious complications associated with intracardiac surgery are hypersecretion in the pulmonary tree and persistent heart block.

Respiratory complications following operation are more frequent in cases with pulmonary hypertension. These patients have excessive thick tenacious mucus in the tracheobronchial tree which they are unable to clear and which frequently causes lung collapse, cyanosis and tachycardia. In these patients, the cardiac and pulmonary reserve is already greatly reduced and hypoxia resulting from blockage of a segment of airway can be rapidly fatal. This sequence is commonest in patients with a large ventricular septal defect, atrioventricular canal or a patent ductus arteriosus of long duration where increased pressure in the pulmonary artery, the result of a large left to right shunt, has produced occlusive changes in the arterioles of the pulmonary vascular bed. In Minneapolis, the postoperative association of bronchial hypersecretion with pulmonary hypertension is so common that in cases where it is anticipated a tracheotomy is done seven to ten days before cardiac by-pass. After intracardiac surgery, the patient is placed on a Bennett partial assistance respirator, which functions through the tracheotomy tube and actually eliminates the physical effort of breathing for several days. This pro-



cedure also allows easy clearing of tracheo-bronchial secretions, obviates the great physical effort of breathing which these patients have, and thereby reduces the work load on a heart already weakened by cardiectomy and surgical oedema.

The second serious complication is persistent heart block. Although there are other factors, many patients develop complete heart block during intracardiac surgery from mechanical injury of the common conduction bundle (bundle of His) as it passes along the postero-inferior margin of the membranous ventricular septum or inferior to a posteriorly placed ventricular septal defect. When septal defects are repaired in an actively beating heart, a suture which has damaged the conduction system and produced heart block can be observed occasionally and its removal may restore normal rhythm. However, when the heart is in potassium arrest it is impossible to observe the offending suture and complete atrioventricular dissociation may be discovered only after the heart beat is restored.

Another type of heart block, difficult to define and not well understood, seems to be present in patients with low cardiac reserve. Thus atrioventricular dissociation during operation occurs frequently in patients with severe pulmonary hypertension where pulmonary pressures exceed 70% of systemic pressures, while in other cases, such as tetralogy of Fallot, where the myocardium is severely hypoxic and the cardiac reserve is reduced, complete heart block may occur before sutures are inserted into the heart.

In many cases, heart block is brief but if it persists after the completion of the operation, active measures must be instituted quickly. Treatment of persisting surgical heart block has been improved by the drug isopropyl levo-arterenol (Isuprel),\* which increases the irritability of ventricular myocardium and speeds its rate of contraction.<sup>10</sup> When heart block persists following closure of intracardiac defects, a 1 in 50,000 solution of Isuprel is given intravenously in 1 to 3 c.c. doses, depending on the patient's age. The ventricle is maintained at approximately 120 beats per minute for several hours postoperatively, following which Isuprel linguets, 5-10 mg. rectally, are given. The maintenance dose is governed by the apex rate and is continued until the heart reverts to sinus rhythm or until an idioventricular rate develops with a stroke volume capable of sustaining systemic pressure and coronary circulation. Some patients have become refractory to the drug within 14-21 days, resulting in a dangerously slow idioventricular rate, reduced coronary circulation, and death from cardiac arrest.

More recently, in the University of Minnesota Hospitals, when heart block persists at operation

a silver-plated copper wire is sutured into the myocardium of the right ventricle, brought out on the chest through a minute stab wound and connected to an electrical cardiac pacemaker set to maintain a ventricular rate of 100 or 110 beats per minute during the critical postoperative period. It has been found advisable to use Isuprel in conjunction with the electrical pacemaker so that in the early postoperative period, if the latter should for some reason fail, Isuprel will usually maintain a satisfactory apex beat. Conversely, if the drug should become less effective the electrical pacemaker will continue to maintain a satisfactory ventricular contraction. As a rule, if sinus rhythm has not returned in a week to ten days, spontaneous idioventricular contractions begin to interfere with the action of the electrical pacemaker, ventricular action becomes irregular, and the use of the electrical stimulator is best terminated. In such cases Isuprel usually continues to have some effect on the heart beat, but gradually the apex rate slows to 50-70 beats per minute, the reduced rate being compensated by an increased stroke volume.

#### COMPLICATIONS OF TOTAL PERFUSION

In addition to the complications of surgery, there are several directly associated with the use of pump-oxygenators and extracorporeal circulation. These complications are metabolic acidosis, bleeding tendencies and blood trauma.

Tissues that are poorly oxygenated produce increased amounts of fixed acids, such as lactic and pyruvic. The result is an acidosis of metabolic origin. In total body perfusion three factors controlling metabolic acidosis and therefore closely related to patient survival, are the rate of perfusion, the level of oxygenation in arterial blood, and the duration of perfusion.

Paneth *et al.*<sup>11</sup> showed in dogs perfused with fully oxygenated blood that a flow of 1.5 litres per square metre body surface per minute was the lowest that would supply the basic metabolic demands of the tissues. At that flow, the difference in oxygen saturation of arterial and venous blood rapidly decreased, the bicarbonate reserve improved as evidenced by a rise in blood pH, and also there was a fall of lactic acid level in the venous blood, when compared to perfusion at lower flow rates.

With 100% oxygenation of arterial blood, the body can tolerate flow rates of less than 1.5 litres per square metre during the 10 to 45 minutes required for corrective intracardiac surgery, but moderate metabolic acidosis may occur. However, reduced oxygenation to 90% or slightly less in arterial blood must be compensated by flows greater than 1.5 litres per square metre if severe acidosis is to be avoided. Mild degrees of metabolic acidosis after total body perfusion are spontaneously corrected by the patient or may be aided by intravenous

\*Winthrop-Stearns Company.

molar lactate. If acidosis is severe, intravenous administration of sodium bicarbonate, 4.5 mEq. per kilogram of body weight, will usually return pH and bicarbonate levels to normal.<sup>12</sup>

The DeWall-Lillehei bubble oxygenator, while having its limitations, is at present the most efficient blood oxygenator and consequently can be used safely at lower flow rates than other types (55 to 45 c.c. per kg. body weight per minute). The time factor, however, is still an important consideration.

Whole blood passing through a pump-oxygenator may be altered by loss of fibrinogen or damage to erythrocytes producing excessive blood haemolysis.

Defibrination of blood can be independent of haemolysis and is not necessarily associated with high levels of plasma haemoglobin. Faulty design or application of filters, bubble traps and tube connectors will rapidly destroy the clotting mechanism of blood by removing fibrinogen and platelets. As a result of faulty equipment, small platelet thrombi upon which heparin has no effect form in dead spaces and at points of turbulence distal to areas of constriction. These friable thrombi may pass into the patient as fibrin emboli and produce cerebral damage; at the same time defibrinated blood, having lost its clotting power, will produce uncontrolled bleeding at the site of operation and in other areas including the brain. This sequence can be prevented if blood streaming through a pump-oxygenator is free from excessive turbulence. To achieve this, all connectors should be highly polished and tapered to a thin edge so that no shoulder exists between tubing and connector; sharp constrictions in the tubing and flagellation of blood by long sock-like mesh filters should be avoided and there should be no glass surfaces in the circuit.

Elevation of plasma haemoglobin levels after total body perfusion is usually the result of excessive blood trauma. After operation, destruction of traumatized erythrocytes may continue to be abnormally high and produce anaemia severe enough to require transfusion.

While renal tubules tolerate a plasma haemoglobin level of 200 mg. %, any level in excess of 60-70 mg. % after one-half hour of total perfusion is an indication for close check of the pump oxygenator.

Excessive blood trauma and its sequelae may be avoided by reducing the number of moving mechanical parts in contact with blood, by avoiding the use of a high pressure blood sucker in the open heart and by reducing the number of times any given cell re-circulates through the apparatus. The latter recommendation is achieved by a large blood volume in the apparatus and by keeping the time of operation to a minimum.

Extracorporeal circulation has made possible great advances in cardiac surgery that will con-

tinue to include various defects previously considered inoperable.

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## GENERAL PRACTICE

### FUNDAMENTALS IN THE CARE OF THE PATIENT WITH RHEUMATOID ARTHRITIS\*

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THE UNFORTUNATE VICTIM of rheumatoid arthritis has long been the despair of many a practising physician. The mysteries of the etiology of this strange and potentially devastating disease remain to be more fully explored and revealed. To date there is no cure, nor yet any single form of treatment which is consistently beneficial to all patients with rheumatoid arthritis. Despite these rather gloomy facts, there is no justification for the defeatist attitude that nothing can be done for patients with this disease. On the contrary, there is convincing evidence that the conscientious application of certain fundamental principles of treatment can permit the majority of people with rheumatoid arthritis to retain or regain normal or nearly normal living.

In recent years important new drugs have been added to the physician's therapeutic resources. Gold salts, ACTH, cortisone, hydrocortisone, prednisone, prednisolone and phenylbutazone have become established as useful adjuncts in the treatment of some patients. While the advent of these drugs has contributed materially to the wellbeing and future outlook

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of some, there is an unfortunate tendency on the part of patients and many physicians as well, to accept these therapeutic agents as self-sufficient, specific forms of treatment at the risk of neglecting more basic fundamentals of therapy. Irrespective of the therapeutic drugs employed, there are certain common-sense principles of treatment which should be practised in appropriate degree by every patient with rheumatoid arthritis.

#### REST

Many patients with this disease are constitutionally ill with such manifestations of systemic illness as malaise, low-grade fever, leukocytosis, anaemia, elevated sedimentation rate, fatigue, weakness, poor appetite and loss of weight. When these constitutional symptoms are severe, total bed rest may be necessary. In milder cases, a few hours' extra bed rest each day may suffice. The amount of rest required cannot be determined by any inflexible formula but must be assessed on the basis of the needs of each patient at any given time during the course of the illness.

#### SPLINTING

Local rest of involved joints, over and above that which is provided by general body rest, is accomplished by the general principle of splinting. There are three common indications for splinting rheumatoid joints. (a) Splinting is indicated at the earliest sign of a developing deformity. (b) It may be used to correct a deformity which has already developed. (c) It may be useful to relieve pain and spasm in an acutely inflamed joint. Many simple methods of joint splinting can be employed satisfactorily in the home. Suitable temporary splinting may be effected by sandbags placed alongside a limb, or splints may be devised from wood, metal or plastic materials. The most convenient type of splint is the slab or gutter splint made from plaster of Paris moulded to hold the limb in the desired position.

Prolonged and uninterrupted immobilization by splints or by any other device is undesirable if joint function is to be maintained. Generally speaking, if splints are used, they should be removed at least once or twice daily to permit the application of heat and the practice of controlled therapeutic exercises.

#### PHYSIOTHERAPY

Although the provision of adequate rest is of fundamental importance, the maintenance and improvement of joint and muscle function is equally essential. To accomplish this objective, the most important aspect of physiotherapy is the regular practice of a program of therapeutic exercises designed to meet the requirements of the individual patient.

#### EXERCISES

##### *Passive Exercises*

Passive exercise, the movement of a joint by someone else while muscles are completely relaxed, is of value in maintaining range of joint movement and preventing contractures and ankylosis.

##### *Active Exercises*

Active exercises are prescribed to maintain and to improve joint movement, muscle bulk and power, and to prevent weakness, atrophy and consequent joint instability. As joint stability is improved, pain-producing stresses are lessened. Reduction of the spasm secondary to pain decreases the likelihood of deformities which develop as a result of spasm in the dominant flexor muscles.

##### *Static or Tension Exercises*

When pain and inflammation are severe, very little movement may be accomplished by active exercises. In such cases, static or muscle-setting exercises may be prescribed until joint pain and inflammation have subsided sufficiently to permit active exercise. Tension exercises are performed by active contraction or tensing of muscle groups such as the quadriceps femoris, for example, without carrying out any actual movement of the joint. Tension exercises can also be practised while a limb remains immobilized in a splint.

##### *Assisted Active Exercises*

When pain and inflammation are less severe but still interfere with adequate active movement, the active exercises performed by the patient may require some form of assistance. This may be provided manually by a physiotherapist or by another attendant or it may be effected by mechanical devices such as slings or suspension apparatus. Under-water exercises are a form of assisted-active exercise in which the assistance is provided by the anti-gravity buoyancy forces of water. Under-water exercises may be carried out in a therapeutic pool or tank or even a bathtub in the home.

##### *Resistance Exercises*

When the arthritic patient has developed good joint mobility and muscle power working actively against gravity, resistance exercises may be introduced. Here, the joint movement is carried out against some form of resistance such as the pressure of an attendant's hand, or weights attached to the limb by special equipment such as Delorme's apparatus, or by the pull of weights over a pulley system. Resistance exercises are very valuable in the treatment of rheumatoid arthritis if prescribed at the proper stage and carefully supervised. They demand more muscle work and develop more muscle bulk and power,

and in this way may contribute materially to joint stability, protection from trauma, and prevention of further joint damage.

#### GENERAL COMMENTS CONCERNING EXERCISES FOR THE PATIENT WITH RHEUMATOID ARTHRITIS

The details of the exercise program must be planned to meet the current needs of the patient. Joint inflammation is rarely so severe as to contraindicate gentle movement of any joint through the full range of which it is capable at least once a day. It is the usual procedure to begin with at least five full movements of each joint daily and to increase the number of repetitions until the desired number of exercises is being performed or until the patient's tolerance is reached. As a rule, the patient begins with active or assisted-active exercises, but as already indicated, in some cases it is necessary to start the exercise program with passive or tension exercises. Increase in joint pain or stiffness during exercise or for a few hours afterwards is not a contraindication to continuing the program. If pain is definitely aggravated and persists throughout the whole day following or if there is increased joint swelling, heat, and tenderness, muscle spasm or tremor, the exercise program must be modified, usually by reducing the number of repetitions of each movement.

#### HEAT

Heat is a useful physiotherapy modality in preparing the arthritic patient to carry out his exercise program more efficiently. Since its maximum physiological effect is attained in about 20 to 30 minutes, the usual practice is to apply local heat for this period of time once or twice daily and to follow this immediately by the program of exercises. There are many simple techniques of applying local heat in the home. An infra-red bulb can be used in a gooseneck or bridge lamp at a distance of 18 to 20 inches from the area to be treated. Home-made radiant heat bakers, electric pads or electric blankets, or even hot water bottles are other sources of surface heat which can be used regularly in the home. If moist heat is desired, it can be provided by hot moist packs, hydrocolator packs or hot baths. Paraffin wax baths provide a satisfactory method of applying local heat to the small joints of the hands and feet and can be prepared simply in the home. Deep heat in the form of short-wave diathermy has no particular advantage over the simpler techniques. In many cases it provides less comfort and in some may even aggravate pain. Ultrasonic therapy is of little value to most patients with rheumatoid arthritis.

#### MASSAGE

Massage has a distinctly limited place in the treatment of this disease. It often induces an

attitude of dependency upon the masseur, resulting in neglect of the active exercises which the patient must perform under his own power. Massage over an actively inflamed joint may be harmful and of course is contraindicated.

#### POSTURAL INSTRUCTION AND PREVENTION OF DEFORMITY

Every patient with rheumatoid arthritis should receive detailed, intensive and oft-repeated instruction in the principles of proper posture until he becomes "posture-conscious" and automatically assumes the optimum posture of which he is capable in all his everyday activities.

The objective of such intensive postural training is to minimize joint strain, particularly the mechanical strain on weight-bearing joints, and to prevent or minimize deformities. Since deformities are much easier to prevent than to correct, postural instruction should be begun as early as possible in the course of the disease. The rheumatoid patient confined to bed for prolonged periods is particularly liable to develop faulty postural habits leading to deformities in several joints. The majority of these common deformities can be avoided by simple precautionary measures. The use of splints for this purpose has already been discussed. Other simple devices to check postural faults and prevent deformities include fracture boards beneath the mattress, foot boards and protective cradles to relieve the pressure of bed clothes and prevent foot-drop, and sandbags to prevent external rotation at the hip. Patients should be warned against the all too prevalent habit of lying with their knees propped up over one or more pillows in a semi-flexed position. Too many pillows beneath the head may also lead to cervical flexion deformity. Every rheumatoid patient confined to bed should spend 15 minutes two or three times each day lying face down with the hips and knees fully extended and the arms abducted and internally rotated. This position, and the exercises which can be carried out from it, may be of considerable value in preventing shoulder, elbow, hip and knee deformities. Regular daily periods during which the elbows are held fully extended also help to prevent elbow flexion deformities.

All of these techniques of physical medicine, the use of heat, exercises, postural instruction and deformity prevention should be planned and integrated into an organized program to meet the needs of each patient. The practitioner should be familiar with the various forms of physiotherapy and should continually stress their value and importance to his arthritic patients. To assist in the detailed instruction and continued supervision necessary in a comprehensive physiotherapy program, the services of an experienced physiotherapist are often of great value. In many instances, physiotherapists in private practice or in hospital employ may not



be accessible to the patient. For this reason, the Canadian Arthritis and Rheumatism Society has developed mobile physiotherapy units which the doctor can call upon to provide instruction and supervision to the arthritic patient in his own home, in those communities where branches of the Society have been established.

#### DRUGS FOR THE RELIEF OF PAIN

Analgesia is another fundamental aspect of treatment of the rheumatoid arthritic patient. Salicylates have long been the most useful and widely used drug in this regard. They may be combined with phenacetin and caffeine if desired, and codeine may be used alone or in combination with aspirin to tide the patient over more painful acute periods of his disease. Codeine should not be used routinely on a long-term basis for patients with a chronic, long-drawn-out disease of this type. Salicylates are generally more effective if given in regular, divided doses to a total of three to five grams each day, rather than at sporadic and irregular intervals dictated by the degree of the patient's discomfort. The possibility of salicylate toxicity must be kept in mind although it is not commonly encountered in adult patients. A small proportion of patients may be unable to tolerate adequate doses of salicylates because of gastrointestinal irritation. Enteric coating, buffering, or combination with amino-acetic acid may minimize the irritating effect of the salicylate sufficiently to permit the majority of persons to continue on regular daily doses. There is no convincing evidence that more expensive combinations of salicylates with drugs such as calcium succinate, para-aminobenzoic acid or any of the vitamins have any greater analgesic or anti-rheumatic effect than aspirin or sodium salicylate alone. Phenylbutazone (Butazolidin) is a more recently developed analgesic drug which may be of value in the treatment of some patients but its potentially serious toxic effects render this drug unsuitable for routine long-term treatment of all rheumatoid patients.

#### DIET

There is no anti-arthritic food and, conversely, no food element or combination of food elements which aggravate rheumatoid arthritis. Overweight patients should be given instruction and constant encouragement in weight reduction by dietary means. Patients who are underweight and in poor nutritional state should be provided with an adequate intake of calories, protein, vitamins and minerals. If the patient's appetite and dietary intake are poor, it is rational to supplement the diet with concentrated protein drinks and polyvitamin preparations, although it should be understood by both patient and doctor that these dietary supplements are not specific forms of therapy for the arthritis. Vitamin C, and concentrated doses of vitamin

D, the latter under the trade name "Ertron", have been reported to have beneficial effects in rheumatoid arthritis but such claims have not been substantiated by subsequent experience.

#### FOCI OF INFECTION

Obvious infections in teeth, tonsils or other sites should be treated adequately as they would be in the patient with no arthritis. Removal of infected foci rarely produces any lasting or appreciable benefit on the rheumatoid process itself. Indiscriminate removal of teeth, tonsils and other organs, in the hope of removing some hidden focus of infection, is not justified.

#### PSYCHOLOGICAL AND SOCIO-ECONOMIC FACTORS

The undesirable effects of psychic and emotional stress upon patients with rheumatoid arthritis are generally recognized. Unfortunately, a chronic, painful, disabling disease of this type often creates a vicious circle imposing new social, domestic, psychological and economic problems which are frequently followed by further aggravation of the underlying organic disease. While the doctor may be unable to do little more than recognize these factors, he would do well to acquaint himself with the various resources in his community which he can call upon to assist in relieving the arthritic patient and his family of many of their social, domestic and economic burdens. Among the agencies which provide assistance in the fields of social service, welfare, vocational guidance, vocational training and job placement are the governmental departments of health, welfare, and education, the National Employment Service, and such voluntary groups as the Canadian Arthritis and Rheumatism Society, the Victorian Order of Nurses, homemaker agencies, occupational therapy associations, and other voluntary organizations of this type. This is but a partial list of such agencies which vary in the variety, number and type of services offered from one community to another.

#### SUMMARY

The basic principles of rest, splinting, exercise, heat, postural training, prevention of deformity, relief of pain, maintenance of optimum nutrition, and the proper treatment of intercurrent infections, constitute a fundamental program which should be employed by every patient with rheumatoid arthritis irrespective of other forms of treatment in use. Constant encouragement and reiteration of the value and importance of such a program are necessary in nearly all cases. It is often difficult to impress patients with the necessity for faithful adherence to these rather undramatic measures, but they are of such fundamental importance that they alone can prevent the majority of deformities and much muscle wasting, weakness and limitation of movement which are so common when these principles are neglected.

## MEDICAL ECONOMICS

## THE INFLUENCE OF WAITING PERIODS ON THE COSTS OF HOSPITAL CARE INSURANCE

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With a view to throwing some light on the influence of waiting periods on probable benefits and costs of any comprehensive hospital care plan, an examination has been made of certain of the data made available by the Hospital Morbidity Study, Ontario, 1951.

*The Influence of an Absolute Waiting Period on Hospital Benefits*

An absolute waiting period is one which applies to all patients regardless of length of stay. It is a device commonly used in many types of insurance in the commercial field. In principle, waiting periods not only provide a deterrent to excessive use of hospital services but also serve as a means whereby comprehensive hospital care coverage can be afforded all persons for extended durations at a much lower cost than would otherwise be the case without such provision, and without placing an undue burden upon any participant.

Under this arrangement, in the case of hospitalization for a period of 14 days, a waiting period of

TABLE I.—EFFECT OF VARIOUS ABSOLUTE WAITING PERIODS ON HOSPITAL BENEFITS  
ONTARIO PUBLIC GENERAL HOSPITAL EXPERIENCE, 1951

Waiting period	Hospital costs modified*				Hospital costs not modified†			
	Patients affected		Days involved		Patients affected		Days involved	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
None.....	542,499	100.0	5,450,091	100.0	0	—	—	—
3 days.....	376,081	69.3	4,028,684	73.9	166,418	30.7	1,421,407	26.1
7 days.....	229,959	42.4	2,850,266	52.3	312,540	57.6	2,599,825	47.7
10 days.....	134,407	24.8	2,271,046	41.7	408,092	75.2	3,179,045	58.3
13 days.....	94,294	17.4	1,913,722	35.1	448,205	82.6	3,536,369	64.9
20 days.....	51,960	9.6	1,406,781	25.8	490,539	90.4	4,043,310	74.2
27 days.....	33,398	6.2	1,106,674	20.3	509,101	93.8	4,343,417	79.7
55 days.....	9,528	1.8	589,078	10.8	532,971	98.2	4,861,013	89.2
3 months.....	3,627	0.7	382,568	7.0	538,872	99.3	5,067,523	93.0

\*Under a hospital care plan with complete coverage from the first day, the introduction of a waiting period of any length would either modify or eliminate all claims.

†Under a hospital care plan with complete coverage, these figures indicate the number of patient's claims and hospital days that would be eliminated by the introduction of absolute waiting periods of various durations.

This subject was first discussed and the general method of analysis involved was first used in Ontario in the Supplement to Part IV of "The Survey of Public General Hospitals in Ontario, 1940", entitled "The Cost of Hospital Care to the Government", which was prepared and published by the Division of Medical Statistics, Ontario Department of Health in 1940.<sup>1</sup> This document dealt with the influence of waiting periods of two types, with particular reference to the saving effected by withholding the grant paid on behalf of self-pay public ward patients.

More recently, certain data have become available from the recently published Hospital Morbidity Study for Ontario which covered the experience of all public general hospitals in Ontario during 1951.<sup>2</sup> This report has afforded a means of assessing the possible influence of waiting periods on the costs of any province-wide all-inclusive hospital care plan, in terms of payment of any given rate of benefit. The present observations are based on the data contained in Tables 3 and 11 of the Hospital Morbidity Study Report, adjustment being made to the duration data by excluding all full-term live-born infants on the assumption that they were in the 4-7 day group.

three days would mean that the individual would pay for the first three days and the hospital care fund would be required to pay the hospital account for the 4th to 14th days, together with any ancillary charges covered under the contract.

The influence of an absolute waiting period on the total hospital days to be financed out of a hospital care fund and the number of patients affected is illustrated by the data presented in Table I.

The figures suggest that a short waiting period of three days for hospital benefits would eliminate from benefits 30.7% (possibly less) of all patients with only 5.4% of the total hospital days, and would modify the benefits of the remaining 376,081 patients (69.3% of the total) to the extent of 3 days per patient, i.e. 1,128,243 days or 20.7% of the total days. In other words, a three-day waiting period would eliminate 30% of patients and roughly one-quarter (26.1%) of all hospital days from benefit coverage—a rather remarkable effect.

It is of interest that in the 1940 Ontario Study based on 1936 data, the proportions of self-pay public ward patients and days of care expected to be excluded from benefit with a three-day waiting period, although lower, were of a similar order—26% of patients and 22% of days.

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# *Restriction of Benefits to Patients with Stay in Excess of a Specified Duration*

In contrast to an absolute waiting period, which affects all patients regardless of length of stay, the limitation of benefits to patients with specified hospitalization durations or greater (benefits retroactive to the first day, after a stated duration) does not relieve the plan of the payment, on behalf of the beneficiary, for days of hospital care of less than the specified duration. The load to be carried by a plan in this situation is therefore much greater than with an absolute waiting period of the same duration. While the object of such a plan is to concentrate benefits in those patient categories for which the hospital financial load is greater, there are certain popular objections and administrative difficulties involved.

contribution is proportionately much smaller the greater the length of stay and their "loss of coverage" is proportionately much less. An absolute waiting period also avoids the administrative objection associated with limiting benefits to patients of a specified duration, namely the potential inducement for discharge to be delayed beyond any specified waiting period, in order to carry the patient into the entitlement interval with complete retroactive benefits.

The application of an absolute waiting period, even one as short as three days, would substantially reduce the cost of any plan, and the premiums (direct or indirect) to be paid by the subscribers, and at the same time the direct costs to the individual patients would be quite modest. This device makes it possible for greater coverage—even com-

TABLE II.—EFFECT OF LIMITING HOSPITAL BENEFITS TO PATIENTS WITH SPECIFIED DURATION OF STAY  
ONTARIO PUBLIC GENERAL HOSPITAL EXPERIENCE, 1951

Hospital stay in excess of	Hospital costs eliminated*				Hospital costs not affected†			
	Patients		Days		Patients		Days	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0 days.....	542,499	100.0	5,450,091	100.0	0	0.0	0	0.0
3 days.....	376,081	69.3	5,156,927	94.6	166,418	30.7	293,164	5.4
7 days.....	229,959	42.4	4,459,979	81.8	312,540	57.6	990,112	18.2
10 days.....	134,407	24.8	3,615,116	66.3	408,092	75.2	1,834,975	33.7
13 days.....	94,294	17.4	3,139,544	57.6	448,205	82.6	2,310,547	42.4
20 days.....	51,960	9.6	2,445,981	44.9	490,539	90.4	3,004,110	55.1
27 days.....	33,398	6.2	2,008,420	36.9	509,101	93.8	3,441,671	63.1
55 days.....	9528	1.8	1,113,118	20.4	532,971	98.2	4,336,973	79.6
3 months.....	3627	0.7	705,371	12.9	538,872	99.3	4,744,720	87.1

\*Under a hospital care plan with complete coverage for all patients from the first day, the introduction of a provision to restrict benefits to patients with a specified duration of stay or longer, would limit the payments to the patients and their days of care indicated.

†These figures represent the patients and their days of care which would be eliminated if hospital care benefits were limited to patients with a specified stay or longer.

The influence of the restriction of hospital care plan benefits to patients with a specified duration of hospital stay or greater is illustrated by the data in Table II.

If hospital benefits were restricted to patients staying in hospital longer than three days, one-quarter of all patients (those staying one to three days) would receive no benefits, but only slightly more than 5% of hospital days would be eliminated from the coverage. In other words, the plan would still cover 95% of hospital days.

## DISCUSSION

An absolute waiting period has a number of advantages over the restriction of benefits to patients with a specified duration of stay or greater, the latter being equivalent simply to having a waiting period but making payments retroactive for those whose stay is in excess of that waiting period.

Of the two alternative procedures, the absolute waiting period is preferable because all patients would contribute relatively small amounts towards their hospital service for each admission regardless of duration of care. Furthermore, although patients whose stay is relatively long would pay amounts equal to those to be paid by short-stay cases, their

plete catastrophic coverage—to be provided at very much lower rates of premium if voluntarily financed, or at a lower cost to the taxpayer if financed out of public funds (i.e. through taxes).

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## LISTENING TO PATIENTS

"One experiment at a hospital connected with Harvard University illustrated the fact that training in rigid, question and answer, history taking had at least temporarily hampered the students' original natural aptitudes for interviewing. In this experiment the same patients on the medical wards were interviewed by senior medical students and senior arts students. The shocking finding was that the senior arts students elicited more information from the patients concerning emotional and social problems relevant to their illnesses than did the medical students! Of course the arts students did not know how to use the information. Nevertheless they appeared to have a skill which the medical students presumably had lost."—*Manitoba M. Rev.*, 37: 439, 1957.

## MEDICAL MEETINGS

## INTERNATIONAL PSYCHIATRY, 1957

*[The two contributions printed below reflect two viewpoints on this year's International Congress of Psychiatry, kindly submitted by two Canadian participants. Both are printed because they complement each other and throw light on different aspects of a many-sided theme—modern psychiatry.—ED.]*

AFTER ZURICH,  
SEPTEMBER 1 TO 7, 1957

HUMPHREY OSMOND, M.D.,\*  
Weyburn, Sask.

The 2500 or more psychiatrists, fellow scientists, their wives and others, who gathered in this ancient town at the beginning of September have now returned whence they came. Karl der Grosse (whom we know better as Charlemagne) continues his brooding watch, threatening as a super-ego, from high up on the Grosse Munster, undisturbed. In Hong Kong and Glasgow, Reykjavik and Melbourne, participants like your correspondent are sorting out their treasure troves of gleanings from plenary sessions, symposia, special sessions, small discussions and the many enjoyable and friendly talks which they had in that memorable week.

What can great jamborees of this sort accomplish apart from a vague sense of camaraderie? Does scientific or any other truth manifest itself to several thousand people, or is it confined to gatherings of two or three only?

The 2nd International Congress of Psychiatry held in September at Zurich will long be remembered in the history of the struggle against schizophrenia, that mighty illness which afflicts with more or less severity at least one per cent of human beings, and fills with a long-staying patient about one of every five hospital beds in the world. At the Congress, papers by doctors from West Africa, Hong Kong and Thailand supported earlier findings which suggest that few cultures are exempt, even though it may seem to afflict modern, long-living, urban man more obviously, though not necessarily more often or more severely than his predecessors.

One hundred years ago Eugene Bleuler, the great Swiss psychiatrist, was born at Zollikon near Zurich. He was a contemporary of Kraepelin and Freud who, with his even more famous pupil Carl Jung, attempted not altogether successfully to combine their ideas. About 1910 he coined the sinister and enigmatic word "schizophrenia" for a group of illnesses which Kraepelin had previously labelled "dementia praecox". Schizophrenia is unfortunately often thought to mean splitting of the mind, though shattering is a better idea. It seems a more suitable term than dementia praecox for an illness which is seen in the old as well as the young and which

is not necessarily accompanied by the mental weakening implied by dementia.

It is typical of Switzerland that the Congress was welcomed by Dr. Manfred Bleuler, himself a distinguished psychiatrist and now director of the Burgholzi in his father's place. What has emerged from the Congress? One can only agree with Dr. Henri Ey of the International Organization of World Congresses for Psychiatry that as yet no synthesis of all views has been achieved. But that would require a miracle, not a congress. How can one reconcile those who consider schizophrenia a way of living with those who look upon it as an illness due to structural damage in the brain? Yet views as divergent as these are held by many who attended the Congress.

There were over 500 listed speakers, many giving several papers. There were plenary sessions galore, special sessions, small discussions, symposia, dinner meetings, film shows, demonstrations, exhibitions, expeditions and outings. How can one summarize such a torrent of talk? Those who had been present at the Paris Congress in 1950 agreed that this was a very different one. Paris was noted for learned and often acrimonious debate. Zurich will be remembered for its account of work done and the foreshadowing of work to be done. In Paris there was scope for every sort of opinion, while at Zurich the presentation of evidence became the main issue. A large number of psychiatrists, biochemists, pharmacologists and other scientists believe that we have growing evidence of what Manfred Bleuler calls "a specific, somatic schizophrenia". In other words, they claim that schizophrenia is a bodily illness of a subtle sort which interferes with the working of the brain. We do not know how much of this evidence will survive the five years or so between Congresses, but few of those at Zurich did not feel that something was stirring, and according to one point of view, this was exciting, disturbing, threatening, even frightening.

It is perhaps a portent of the growing co-operation between different sciences in the exploration of the mind that at Zurich this year the Collegium Internationale of Neuro-Psychopharmacology was founded. Professor E. Rothlin of Basle, the steersman of this group, brought it together with that determined diplomacy for which his countrymen are justly famous. Although only a little was seen at the plenary sessions of the pharmacologists and biochemists, they played a large part in several notable symposia, of which the outstanding ones were those of Professor F. Georgi of Basle on the pathophysiological aspects of psychoses and of Dr. Max Rinkel of Boston on chemical concepts of psychoses. It was a misfortune that in the Second Symposium time was so short that speakers had to be cut by half or more, because new work of the more exciting kind was reported. In these symposia there were many notable moments, such as Dr. Stephen Sherwood's report that impulses in the brain of schizophrenic people travel at a different speed from those of normal people. If this is con-

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firmed it will be the first clearcut indication that schizophrenia is a disease affecting the working of the brain. Or when Dr. Robert Heath of Tulane, Louisiana, described a protein substance found in the blood of schizophrenics but not in normals, which, as his vivid films show, produced a schizophrenic-like condition when injected into volunteers. Or when Dr. A. Hoffer of Saskatoon told of adrenochrome and adrenolutin, the immediate derivatives of adrenaline, which seem to be produced by Dr. Heath's protein and which themselves cause psychotic-like symptoms in volunteers.

This work is only starting. It must be confirmed by others and expanded. No one can tell whether it will stand the test of time, but it was fitting that Dr. Rinkel's symposium should have for its honorary president the great Carl Jung of Zurich. It was he who, over half a century ago, most vigorously emphasized that schizophrenia, for all its psychological manifestations, was an illness produced by a nerve poison which he called Toxin-X. He stuck to this opinion in spite of very strong pressure from Freud and his friends to give precedence to early life experience, and disagreement about this led to his secession from psychoanalysis.

There is further evidence of a change in emphasis in psychiatry in the very large symposium (a gargantuan rather than a Socratic feast) under the chairmanship of Dr. Nathan Kline of New York on the pharmacological treatment of schizophrenia, where there was much discussion about the uses and abuses of that rapidly growing family of drugs called tranquilizers.

The most disappointing feature of the Congress was a lack of much attention to the hundreds of thousands of long-stay patients in mental hospitals. This was particularly disappointing because at both opening and closing sessions the human needs of the sick received eloquent discussion, and it might have been appropriate to emphasize the care of these people. An outstanding paper on the last day from Dr. Freudenberg of Netherne Hospital emphasized how much this subject was neglected at the Congress. The representation of the social sciences was scanty and they made no impression comparable with the biological sciences. One suspects, perhaps unworthily, that while psychiatrists may have at least realized they cannot be their own chemists, they are still more or less unwilling to admit that psychiatric qualification does not necessarily assist in social research. Several sessions purporting to discuss anthropology and mental illness seemed to be more concerned with speculative, clinical chitchat. There appears to be a difference in meaning between the European and Anglo-American use of the word "anthropology". One can only hope that future congresses will devote much more of their time to the care of the long-staying patients. There is no point in psychiatrists talking big about solving industrial and international tensions when the hospitals for which they are directly responsible are often very little better than they were a century ago. We cannot rest until mental

hospitals fulfil Florence Nightingale's first principle, "to do the sick no harm".

And what can be learnt for future gatherings of this sort? Our hosts, whose expertise in such matters is unrivalled, ran the bread-and-butter side of the Congress excellently. Swiss skill and tact was everywhere and we shall not easily forget the patience, kindness and thoughtfulness of our Zurich friends. The organization of the academic part of the Congress was, however, less satisfactory, perhaps because the organizers were keen to hurt no feelings. For instance, there was no agreement about the function of the plenary sessions. Some speakers engaged in broad generalizations while others presented details of experimental work obviously requiring discussion. Much time was wasted by having some speakers repeat their papers in as many as three languages. This was unnecessary with a translating system. Furthermore, several speakers were far less polylingual than they supposed.

The organizers of any future Congress must surely pay much more attention to those two excellent bulletins on the organization of international meetings put out by the Council of International Organizations and Medical Sciences in their July-December, 1956, and January-December, 1957, issues. It is unreasonable to expect people to absorb five or six lectures in a morning. If they are of the right calibre two or, at the very most, three are quite enough. Discussion panels and other devices long used in public education should be more thoroughly employed. It is absurd that those whose work so closely concerns communication between human beings should continue to communicate with each other by stereotyped lectures whose inefficiency has long been known.

So after Zurich we recall many genial colleagues whom it was a pleasure to meet, we remember the hospitality of our Swiss friends with gratitude, and we ruminate on the baffling puzzle of human communication.

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## BIOCHEMICAL RESEARCH IN PSYCHIATRY

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Montreal

The 2nd International Congress for Psychiatry, which was held in Zurich at the beginning of September, bore witness to the expanding role which biochemistry is playing in research into mental disease. Two symposia, occupying seven sessions of the Congress, were devoted to papers of predominantly biochemical and physiological import. The first of these, entitled "Chemical Concepts of Psychosis", was organized by Rinkel (Boston); the second, concerned with "Pathophysiological Aspects of Psychoses", was arranged by Georgi (Basle)

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and Mall (Landau). A series of papers on psychoneuroendocrinology, invited by Reiss (Epsom), were oriented more towards the clinical aspects of the subject. In this résumé some indication will be given of a few of the topics discussed at these meetings, and of the results reported, in order to illustrate current trends in fundamental scientific research in psychiatry.

**Hallucinogens:** Hofmann (Basle), whose discovery of the hallucinogenic properties of LSD (lysergic acid diethylamide) in 1943 sparked the current phase of interest in psychopharmacology, spoke on the relation between chemical structure and biological activity of the ergot alkaloids, of which LSD is an example. Of the four isomers of LSD only one has the specific and potent psychological actions. Cerletti (Basle) discussed views on the mode of action of LSD. He favoured the hypothesis that LSD acts directly on some structures within the central nervous system, perhaps exerting there a "trigger" action. The site of action of LSD may be in the diencephalon. Cahn (Philadelphia) reported on electroencephalographic changes in rabbits induced by chronic administration of LSD. With large doses there is a reduced rate of carbohydrate oxidation by the brain. Harley-Mason, Laird and Smythies (Cambridge) have found that mescaline follows different routes of metabolism in man and experimental animals. One of the early products in human urine is a demethylated, oxidized derivative (3, 4-dihydroxy-5-methoxyphenylacetic acid), conjugated with glutamine. Zeller (Chicago) stated that diamine oxidase (histaminase) acts upon mescaline.

**Tranquillizers:** Brodie (Bethesda), in whose laboratory it was found two years ago that reserpine causes the release of serotonin (5-HT or 5-hydroxytryptamine) from bound sites (as it is ordinarily held in the brain, intestine, platelets, and elsewhere), presented a theory of the role of serotonin and noradrenaline in brain function. He considers that noradrenaline (given intrathecally), Ritalin and iproniazid (Marsilid) all exert actions on the ergotrophic system of Hess. On the other hand, reserpine causes trophotropic symptoms (sedation, EEG sleep patterns). LSD blocks this system. Pletscher (Basle) described a new series of synthetic compounds, benzoquinolizines, which, like rauwolfia alkaloids, cause the release of 5HT and noradrenaline in the brain. Their duration of activity and intensity of action are less pronounced than those of reserpine, but their pharmacological actions are similarly antagonized by Marsilid, an amine oxidase inhibitor. Voelkel (Berlin) reported on the clinical uses of Tetrabenazine, one of the benzoquinolizines. Its sedative non-hypnotic action has been found useful in paranoid-hallucinatory psychoses, in the climacterium, and in involutional cases. Higher doses cause an akinetic-abulic syndrome somewhat like, but not identical with, that seen with reserpine. Cleghorn, Sloane and Saffran (Montreal) reported on the influence of chlorpromazine on corticosteroid excretion. No consistent effect of the drug was found on the resting level

of cortical hormone in the urine of mental patients. However, chlorpromazine reduced the increased output of corticosteroids following intravenous administration of ACTH.

**Hormones:** Several papers dealt with the physiology of periodic catatonia (Danziger and Elmergreen (Milwaukee); Froeshaug (Asker); and Richter (Baltimore) and the therapeutic effectiveness of thyroid therapy in this condition (Danziger; and Gornall (Toronto)). Strauss and Stevenson (London) reported on the use of dehydroisoandrosterone (Diandrone) in the treatment of depressive patients. Studies on catecholamine metabolism in mental patients indicate that subjects having a low rate of urinary excretion of these compounds (predominantly adrenaline and noradrenaline) tend to improve as a result of electroconvulsive therapy, in contrast to the poorer results with patients whose rate is high (Sourkes, Montreal). Bullmore, Reiss and Smith (Epsom) found only a small percentage of the mental patients in a male juvenile unit to be in normal hormonal equilibrium. Sixteen per cent showed abnormalities of thyroid function; others showed disturbances of growth and gonadal function.

**Toxic factors in psychoses:** Considerable attention was devoted at the Congress to the attempts to implicate specific chemical factors in schizophrenia and other mental diseases. Hoffer (Saskatoon) restated the hypothesis that adrenochrome and adrenolutin, or similar compounds, play an etiological role in psychoses. Woolley (New York) thinks that schizophrenia is due to a defect in serotonin metabolism, probably resulting in a deficiency of this substance in the brain. Bulle (Washington) takes the opposite view, namely, that schizophrenia is due to an overproduction of serotonin, which serves to depress the higher cortical centres. In manic-depressive psychosis, the depressive phase would be due to excessive serotonin, the manic phase to excessive noradrenaline. Among 52 cerebrospinal fluids examined, only those obtained from schizophrenics contained a serotonin-like substance. The "indole theories" of psychosis have prompted a search for abnormal excretory patterns of indoles. However, several investigators reported no qualitative differences in these respects between urines from schizophrenic patients and from non-schizophrenic subjects (Curzon (London); Buscaino and Stefanacchi (Siena); Sano (Osaka); and Honegger (Basle)). Zeller (Chicago) measured only the excretion of 5-hydroxyindolacetic acid, an important metabolic derivative of serotonin, in the urine, and found no difference between the amounts in urine of schizophrenics and controls. However, the former excreted more of this acid than the non-schizophrenic after receiving a test load of tryptophan, the primary precursor of serotonin in the body. Schwarzenbach (Basle), using mould sporulation tests, and Rieder (Basle), using the spider's web test, have found active material in schizophrenics' urine (extracted by Honegger's methods) which is not found in normal urines. Streifler, Kornbluth and Wertheimer (Jerusalem) observed a depression of



glucose oxidation by rat retina (i.e., neural tissue) in the presence of serum obtained from schizophrenic patients. With normal serum there is a rise in the oxidative rate. The bile of certain schizophrenics contains a heat-labile substance capable of causing experimental catatonia in animals (Baruk, Paris). A similar effect is obtained with bile collected from patients with serious migraines, icterus or chronic rheumatism. According to Mall (Landau) many epileptic and schizophrenic patients contain a toxic substance in their serum, associated with the globulin fraction, which causes convulsions or death on injection into mice. Mall suggests that normal serum has protective colloids, perhaps in the albumin fraction, which prevent the rapid hydrolysis of the toxic compound from the globulin. Haavaldsen, Lingjaerde and Walaas (Oslo) reported on a substance in  $\alpha_1$ -globulin fraction of the serum of some psychotics (especially schizophrenics with disturbed carbohydrate metabolism) which inhibits the uptake of glucose *in vitro* by rat diaphragm. Health (New Orleans) described a substance, which he has called taraxein, occurring in the blood of schizophrenic subjects, but not in normals. On injection it causes EEG changes in the brain of monkey. Human volunteers receiving it exhibit catatonic-like behaviour.

Many other papers dealt in one way or another with the role of physiological factors in mental illness. One could justly depart from the Congress with the strong impression that biochemical theory is now being applied in many quarters to psychiatry just as in the past to other branches of medicine, and that the introduction of the research techniques of biochemistry and physiology into the laboratory of the mental hospital has already yielded many new and useful data about mental disease.

## SYMPOSIUM ON NUCLEAR SEX

There has been a renewed interest in the study of sex anomalies during the past three to four years, largely because of the recently developed tests of chromosomal sex. A large number of papers dealing with various aspects of this work have appeared in journals devoted to a wide variety of disciplines. A group of scientists in the United Kingdom conceived the idea that a representation from those who study nuclear cytology and sex anomalies should be brought together to assess the current status of research in this rather broad field. Accordingly, a Symposium on Nuclear Sex was held at King's College Hospital Medical School, London, on September 6 and 7, 1957. The organizing committee consisted of Dr. W. M. Davidson and Dr. D. Robertson Smith (King's College Hospital), Dr. P. M. F. Bishop and Dr. P. E. Polani (Guy's Hospital), Dr. L. S. Penrose (University College, London), Dr. G. I. M. Swyer (University College, London), and Dr. B. Lennox (Glasgow). Dr. Robertson Smith served as secretary of the committee. There were about seventy participants and

eleven countries were represented (Austria, Britain, Canada, Denmark, France, Germany, Israel, Italy, Portugal, Switzerland and the United States). The Symposium was divided into three sections that dealt with cytology, clinical aspects of sex anomalies, and the sex chromatin in cancer cells. There follows a brief summary of the papers within each section.

### 1. Cytological and Genetic Aspects of Nuclear Sex (Chairman: Dr. L. S. Penrose)

Dr. B. Slizynski (Institute of Animal Genetics, Edinburgh) thought that the recorded figures for the incidence of sex chromatin in sections of female tissues (60-80%) could be explained by an inconstancy in chromosome number and by changing metabolic activities within the cell. It was emphasized in discussion that precise figures for the incidence of sex chromatin in a population of cells are not available. These need to be obtained from material of the highest technical quality, using either whole amounts of thin membranes or by correcting for the thickness of sections in relation to the diameter of nuclei. Dr. C. E. Ford (Atomic Energy Research Establishment, Harwell) discussed human chromosomes, in particular the evidence for a diploid number of 46 rather than 48 and for inconstant pairing of the X and Y chromosomes. He stressed the need for much more detailed knowledge with respect to the morphology of human chromosomes and was optimistic that techniques to achieve this are rapidly becoming available. Mr. H. P. Klinger (University of Basle) described the detailed structure of female sex chromatin using a modified staining technique that clarifies its structure by mild acid hydrolysis. He stressed the double nature of the sex chromatin, which supports the view that it represents the heterochromatin of the two X-chromosomes. The division of the sex chromatin prior to amitotic division of nuclei in fetal membranes was also described. Mr. J. L. Hamerton (Natural History Museum, London) showed that normal pairing and chiasma formation occurs regularly between the homologous segments of the X and Y chromosomes in *Rattus natalensis*, but felt that there were insufficient data to generalize this observation to other mammals. Dr. C. Leuchtenberger (Western Reserve University, Cleveland) presented a quantitative study in which microspectrophotometric and interferometric determinations of desoxyribose nucleic acid (DNA), arginine and dry mass were made on several thousand individual sperm nuclei from fertile men and fertile bulls. While the DNA content and dry mass were very similar for both bull and human sperm nuclei, there was a striking difference in the arginine content, which was about 80% less in human than in bull sperm. Dr. L. Sachs and Dr. M. Danon (Weizmann Institute of Science, Rehovoth, Israel) presented evidence in support of the genetic origin of sex anomalies. Genetic factors were described as operating at various levels, as follows: (a) on the development of the gonad itself (gonadal agenesis and the abnormal gonad of Klinefelter's syndrome), (b) on a definite step in the synthesis of steroid hormones (adrenogenital syndrome) and (c) on tissue response to hormones (testicular feminization syndrome of Morris). They also presented preliminary evidence for a nuclear mosaicism (XX and XO) in some cases of gonadal agenesis and for an unusual sex chromosome complex (XXY) in the testicular feminization syndrome. Dr. P. Riis (Gentofte, Denmark) showed that the sex chromatin of lymphocytes becomes unmasked as pyknotic nuclei change to vesicular nuclei *in vitro*.

### 2. Application to the Study of Intersex and Related States (Chairman: Dr. P. M. F. Bishop)

Dr. M. Danon and Dr. L. Sachs discussed the role of the sex chromosomes in abnormal sex differentiation. Their primary role is to direct gonadal differentiation and when they fail in this respect the phenotypical sex may be at variance with the chromosomal sex, as in gonadal agenesis (Turner's syndrome) and Klinefelter's

syndrome. Dr. A. Prader (Zurich) described a new congenital syndrome in boys where there is lipid adrenal hyperplasia, adrenal insufficiency and feminization. The syndrome was thought to be caused by hereditary enzymatic failure of steroid synthesis in the adrenal cortex and in the Leydig cells of the testis. Dr. C. Overzier (Mainz, Germany) offered a classification of intersexual states. He also presented evidence that the first anlage of the gonads effects an "initial induction" on the primordia of the Wolffian and Mullerian ducts while the more fully developed gonads effect a "permanent induction" on the system of reproductive ducts. He felt that certain variations in the gonadal agenesis or gonadal dysgenesis syndrome depend on whether the initial or the permanent induction was at fault. Dr. E. Slater (Maudsley Hospital, London) confirmed earlier reports that there is agreement between chromosomal and somatic sex in homosexuals and transvestites. Family studies of sex deviates showed that they were likely to occupy a late position in the sibship. Dr. C. N. Armstrong (Newcastle-on-Tyne) gave a detailed case history of a male transvestite. He felt that psychological factors probably contributed in causation but that the specific factor was probably a constitutional one on a genetic basis. Dr. W. M. Davidson and Dr. D. Robertson Smith reported that, in patients with Klinefelter's syndrome and female nuclei in oral smears, the incidence of nuclei with "drumsticks" was lower than in females generally. The cause of this discrepancy was obscure but it was not due to a shift to the left in the Arneith index. Dr. H. R. Wiedemann (Krefeld, Germany) presented data derived from use of the neutrophil test of chromosomal sex in a large series of subjects. Difficulties were encountered only in Klinefelter's syndrome where the need for further comparative examination by different methods of chromosomal sex detection was stressed. Dr. B. Lennox, Dr. M. A. Ferguson Smith, Mr. W. S. Mack and Dr. J. S. S. Stewart (Glasgow) described patients with Klinefelter's syndrome who were encountered in a male infertility clinic. The testicular pathology was distinctly different depending on whether the patient's nuclei were female or male. In chromosomal females, the seminiferous tubules were more abnormal, with much hyalinization, and the Leydig cells occurred in large clumps. It was estimated that of all men who attended the clinic, with any degree of oligospermia, about one in 30 was a chromosomal female. Dr. R. E. Siebenmann (Zurich) further emphasized the relative constancy of the severe testicular abnormality that characterizes Klinefelter's syndrome with female nuclei, in contrast to the variable and less severe testicular histopathology in patients with male nuclei. Dr. J. S. S. Stewart, Miss M. Izatt, Dr. M. A. Ferguson Smith, Dr. B. Lennox and Mr. W. S. Mack presented a family study in relation to Klinefelter's syndrome. A high incidence of sterility was found among uncles of patients, paternal uncles being affected when the patients had female nuclei, and maternal uncles when the patients had male nuclei. They postulated a hereditary mechanism, based on a translocation between autosomes, involving the masculinizing (M) genes. Dr. P. E. Polani, Dr. P. M. F. Bishop and the Glasgow group reported that the incidence of colour blindness in patients with Klinefelter's syndrome agreed with the sex chromosome constitution (XX or XY) as inferred from the cytological tests of sex. Dr. D. J. B. Ashley (Liverpool) described a patient with ovarian tissue only (so far as could be ascertained) and male nuclei in skin biopsy specimens and oral smears.

### 3. *Application to the Study of Tumours* (Chairman: Dr. M. L. Barr)

Dr. N. B. Atkin (Mount Vernon Hospital, Northwood) reported on chromosomes and sex chromatin in squash preparations of human cancer cells from female hosts. Study of the sex chromatin gave some indication of the number of XX sex chromosome complexes in individual nuclei. In particular, two masses of sex chromatin coincided with evidence of tetraploidy from other sources. Dr. A. S. Tavares (Porto, Portugal) found

that the incidence of nuclei with sex chromatin was highly variable in undifferentiated-cell carcinomata from female hosts, in contrast to differentiated-cell carcinomata where the incidence of nuclei with sex chromatin was similar to that of normal tissues. Dr. Lois Myers (Middlesex Hospital) presented a study of nuclei in teratomata. The nuclei were female in tumours from female hosts, although some difficulty was encountered in the interpretation of highly malignant teratomata. For the most part, the nuclei in tumours from male hosts were typically male in some specimens and typically female in others. However, some testicular tumours were encountered with male nuclei in certain tissues and female nuclei in other tissues, of the same specimen. Discussants felt that the latter observation did not necessarily invalidate the etiological theories of Hunter and Lennox, and Tavares (both theories having haploid cells as their starting point) when nuclear structure in highly malignant cells and technical difficulties are taken into consideration.

A committee was appointed to consider revision of the terminology of sex anomalies and their classification. The Symposium closed with a general summary by Dr. M. L. Barr (London, Ontario).

The Ciba Foundation entertained the members of the Symposium at a reception. They were also guests at a dinner given by King's College Hospital Medical School, at which Dr. Robert Platt, President of the Royal College of Physicians, was the principal speaker.

## CANADIAN CONFERENCE ON NURSING

The Faculty of Medicine Building, University of Ottawa, in Ottawa, was the site where about 100 leading health authorities, representing nurses, doctors, hospitals, governments, voluntary agencies and others, spent two days, November 4 and 5, discussing many problems related to nursing education and the provision of nursing services in our present social structure. Mr. Joseph Jeffery, O.B.E., Q.C., President of the London Life Insurance Company, chaired the meeting.

The conference was opened by three introductory addresses. Dr. Burns Roth, Deputy Minister of the Department of Public Health, Saskatchewan, gave the point of view of the doctor-administrator and spoke on "Nursing in Canada, Today and Tomorrow—Problem and Challenge". He pointed out the need for a clarification of the role of the nurse in accordance with the needs of the patient and the technical advances available to good nursing care. In considering various facets for re-evaluation, Dr. Roth said that consideration of the patient's point of view was necessary, as well as a better understanding of the relationship of environmental and emotional factors to ill health. There was need for greater public awareness of nursing problems and their solutions. Dr. Roth recommended studies to determine why young women enter nursing, as a means to improve recruitment. He also suggested that job analysis, to provide better utilization of nursing services, should be carried out, and stated that there is need for a closer co-operation and rela-

(Continued on page 1140)





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*(Continued from page 1138)*

tionship between the nursing profession and other health professions and services.

Mrs. A. Isobel MacLeod, Director of Nursing and Principal of the School of Nursing, the Montreal General Hospital, described the qualities and functions of a good nurse and the importance of reviewing the educational requirements of nurses. She stressed the importance of the nurse as a member of the health team, and emphasized the need for research to define more precisely the role that the nurse should play in medical treatment and health services, so that her education might be designed to that end. Mrs. MacLeod listed several questions for study and evaluation in the nursing program, such as: how can patient care in the home and the hospital be brought more closely together? how can nursing services in the home be financed? how can communications between doctors and nurses be improved? how can nursing services be more effective or better utilized? how can the nurses' work, remuneration, and living accommodation be made more attractive? Mrs. MacLeod also raised several other points concerning the education of nurses, and discussed the use of hospital training schools and university programs as they apply to current needs and changing concepts of nursing services.

Mrs. Rex Eaton, O.B.E., President of the National Council of Women of Canada, presented the point of view of the lay public and stressed the importance of providing practical nursing assistance in hospitals as well as graduate nursing services. She extolled the virtues of nursing and mentioned the high place of the nursing profession in the public mind. Mrs. Eaton raised the question of improving salaries and conditions of work for nurses; this is necessary if employers expect to attract and hold good personnel. She predicted that universal hospital care under the National Hospital Insurance Program would require more nursing personnel, and suggested that the rank and file of nurses should have some method of bringing their problems to hospital boards and the public.

Following the introductory addresses, the members attending the Conference were divided into eight study groups to discuss the broad areas of nursing education, financial implications of training and remuneration, the utilization of nursing personnel, communication between nurses and other health persons, and research in nursing.

One full day of intensive discussion was allowed for study groups; the last half day was devoted to summing up. Miss Helen McArthur, National Director, Nursing Services, The Canadian Red Cross Society, summed up what the patient, the doctor, the government, the parent, the hospital, the student nurse and others expected of nursing services. Reports from the various discussion groups were reviewed by Miss Dorothy Percy, Chief Nursing Consultant, Department of National Health and Welfare, who outlined some of the thinking that had prevailed during the discussion period. These thoughts were consolidated into a number of recom-

mendations from the various groups which were presented by Dr. Malcolm Taylor, Associate Professor, Department of Political Economy, University of Toronto. The following recommendations were approved by the Conference:

1. That the preparation of the nurse should be an educational experience; the method by which this can best be achieved is through a school which plans and controls the complete educational experience of the student.

2. That the budget of a hospital school of nursing should be a separate entity within the over-all hospital budget. Where necessary, budgets should be expanded to enable schools to achieve recognized standards of nursing education. It is further urged that the budget be interpreted to nursing executives, medical staff, hospital administrators, hospital boards and government at all levels.

3. Because the provision of adequate nursing service is of concern to the public, and because of the present lack of factual data on which an assessment of nursing service can be made, it is recommended that research projects be undertaken by interested agencies directed to, among others, the following objectives: (a) the needs of the public for nursing service; (b) the types of personnel now engaged in meeting these needs and duties assigned to them; (c) the possibilities of re-assignment of nursing duties to existing and new groups of nursing personnel; (d) the best and most economic ways of preparing the necessary personnel.

4. There is need for fundamental research and study in other aspects of nursing service and education, and the Canadian Nurses' Association should exercise greater leadership in the launching of such projects.

In addition there is a lack of general knowledge of the findings of past studies and it is recommended that all agencies (schools of nursing, hospitals, and other health agencies) report and interpret their findings to all groups concerned.

5. Because the critical shortage of nurses with advanced training (e.g. teachers, supervisors, administrators, consultants and other specialties) is impeding the recruitment and training of more nurses, it is recommended that the Canadian Nurses' Association investigate methods of expanding the recruitment, selection and training of nurses for advanced studies in these fields. It is further recommended that educational programs be established in these fields at one or more Canadian universities for nurses with a bachelor degree, and that bursary programs be expanded to assist individuals to take advanced training.

6. It is recommended that, in all planning for nursing education, the preparation of the nursing assistant be included as an integral part of nursing education.

7. It is recommended that the Canadian Nurses' Association take steps to improve liaison at local, provincial and national levels with The Canadian Medical Association, the Canadian Hospital Asso-



ciation, the Canadian Public Health Association, and government and other agencies.

8. In view of the greater delegation to nurses of technical procedures formerly performed by the physician, it is recommended that the pressures of scientific techniques and of special skills and other intricacies of modern therapy be not allowed to submerge the art of nursing, i.e. the constant awareness of the importance of the human relationship in the achievement, maintenance and recovery of health.

9. In the expanding hospital care program, more attention should be given to the provision of nursing care in the home as a means of achieving more effective use of hospital and nursing resources.

It was the consensus that the two days of intensive discussion had been useful in reappraising the place of the nurse as a member of the health team, and served to make all those present aware of the evolution that nursing education and nursing services are undergoing as the nurse seeks to find her place in relation to other members of the health professions and agencies in a changing social structure.

#### CANADIAN PSYCHOANALYTIC SOCIETY

On August 1, 1957, at the XXth International Congress of Psychoanalysis, held in Paris, the Canadian Psychoanalytic Society was granted official status of a Component Society of the International Psychoanalytic Association, with exclusive responsibility and power to train psychoanalysts in Canada.

At the Annual General Meeting held in Montreal on October 5, the following Executive Council was elected for 1958: Dr. J. B. Boulanger, President; Dr. J. Aufreiter, Vice-President; Dr. W. C. M. Scott, Secretary; Mr. A. Lussier, Treasurer; Dr. M. Prados and Dr. A. W. MacLeod, Councillors.

At a Scientific Meeting held in Montreal on

October 17, Dr. J. Aufreiter delivered a paper entitled "Some Remarks about Consciousness".

J. B. BOULANGER

#### SCHOOL OF HYGIENE ALUMNI ASSOCIATION, UNIVERSITY OF TORONTO

At a breakfast meeting of this newly constituted Association, held in Cleveland on November 13, 1957, during the annual meeting of the American Public Health Association, the following officers were elected for 1957-58: President, Dr. J. H. Baillie, Toronto; Vice-President, Dr. G. F. Amyot, Victoria; Secretary-Treasurer, Dr. D. L. MacLean, Toronto. Dr. R. D. Defries, formerly the Director of the School of Hygiene, was elected Honorary President of the Association and Dr. F. W. Jackson of Winnipeg the first Senior Member.

### Association Notes

#### C.M.A.-B.M.A. ANNUAL MEETING EDINBURGH, JULY 18-25, 1959

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## LETTERS TO THE EDITOR

### GENERAL PRACTICE

#### *To the Editor:*

And there was much talk in the land.

And those on the high level spoke to those below and said: Now you will work, and you will work hard. You will apply yourselves, and you will study intensively and long. And you will take examinations both oral and written to prove your competence.

And those below were moved by fear and did answer: yea. And they worked long and hard and proved their competence and were conferred with degrees. And they went out into the land and did heal and do good.

Again they did hear the voice from a new high level which spoke to them and said: Now you will work hard. You will apply yourselves and you will study intensively and long, and you will take examinations both oral and written to prove your competence again.

And those below were moved not at all and did answer: Get lost. And they did continue in their own way, and did heal and do good. And there was much talk in the land.

NOTT HOBBS

November 17, 1957.

Dr. Barclay is survived by his widow and two daughters.

DR. COREY SELDON BEZANSON, aged 60, died at his home in Aylesford, N.S., after an illness of several months. He was born in Farmington, Lunenburg County, and was the son of William and Annie Davis Bezanson. He graduated from the Mount Hermon College, Massachusetts, attended Acadia University and later graduated from Dalhousie University in 1922 with the degree of M.D., C.M.

Throughout his lifetime Dr. Bezanson took an active part in community affairs and in the medical societies, not only the Valley Medical Society but the Provincial as well, and was a member of the Canadian Medical Association. For the past 16 years he had served as a municipal councillor in Kings County, and was chairman of the building committee of the municipal school board.

For many years Dr. Bezanson had been interested in the cranberry industry, and had developed three large cranberry bogs. These cranberry bogs were a proud achievement of his and he invented several new picking machines to speed up the gathering of the cranberry harvest. Among his hobbies, Dr. Bezanson devoted some time to operating kennels of Samoyed dogs, and showed champions in Canadian dog shows and also in the United States.

He is survived by his widow, the former Gladys Troop, a sister, Mrs. Clarence Veniot, and a brother, Arthur Bezanson of Berwick.

## OBITUARIES

DR. GIDEON OUSELEY BARCLAY, 78, a medical practitioner in Ottawa for nearly half a century, died at his home there on November 6. He graduated from the University of Toronto in 1909, and practised in Toronto for some years before going to Ottawa. Dr. Barclay was for some years medical superintendent of the Salvation Army Grace Hospital, and served on the consulting staff of the Civic Hospital.

DR. HUBERT-DOMINIQUE BRASSARD, 78, a well-known physician at Roberval, Que., died at his home there on October 27. He was born at Jonquière, Que. After his graduation from Laval University, Quebec, in 1904, he set up practice at Roberval. He was one of the founders of the Hôtel-Dieu Hospital. In 1926 he went to New York where he did postgraduate work in surgery.

He is survived by his widow, four daughters and four sons.

## FELLOWSHIPS in MEDICAL RESEARCH and in PREVENTIVE MEDICINE

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School of Hygiene, University of Toronto.

DR. MALCOLM GEORGE GRAHAM, 67, a general practitioner at West Elgin, Ont., died in the St. Thomas-Elgin General Hospital on November 2. After graduating from the University of Toronto in 1916 he served overseas during World War I. On his return he practised in Exeter, Ont., until 1929 when he went to Formosa. He was in charge of a hospital at Taihoku until 1935. After he returned to Canada Dr. Graham practised at Dutton, Ont.

He is survived by his widow and one son.

DR. LOUISA HART, 87, who served as a medical missionary in India for more than 40 years, died in the Sackville Memorial Hospital, Sackville, N.B., on October 31. She was born in Shelburne, N.S. In 1894 she graduated from the Women's Medical College, New York. During her years in India Dr. Hart was a leader in the development of preventive medicine. She retired in 1938.

She is survived by four sisters and a brother.

DR. EVERETT S. HICKS, 82, surgeon and founder of the Brantford Clinic, Brantford, Ont., died on October 28. In 1896 he graduated from the University of Toronto and later did postgraduate work in England and in the United States. Dr. Hicks founded the Brantford Clinic in 1922 and had studied hospitals throughout the world. He practised surgery at the Brantford General Hospital, the Willett Hospital, Paris, the Norfolk General Hospital and the Tillsonburg Memorial Hospital.

Dr. Hicks is survived by his widow and four daughters.

## PROVINCIAL NEWS

### QUEBEC

Another major hospital change-over has taken place in Montreal. On Sunday, October 20, the new St. Justine Hospital for Children was inaugurated by mass transfer of the 220 patients from the old quarters on St. Denis Street. The move followed extensive planning by the staff of the hospital and traffic police. Thirty-five ambulances made the move in some three and a half hours and without a hitch. Those assisting included the Montreal and Outremont police, No. 1 Medical Battalion (R.C.A.M.C.), F.M.R. reserves, St. John Ambulance, Quebec Society for Crippled Children, Girl Guides and many private firms.

The new building, on the northern slopes of Mount Royal, has been described as a model hospital for children. It has a capacity of 860 beds and 70 bassinets. The estimate is that it will handle 20,000 in-patients per year. No room contains more than four beds, and all rooms are equipped with oxygen and suction ducts and an intercommunication system. There are 20 operating rooms and four delivery rooms. The main feature of the building, shaped like two Y's joined at the base,\* is that it has plenty of daytime light.

The old quarters on St. Denis Street have been sold to the provincial government and may become a hospital for incurables.

Professor John Bruce, C.B.E., head of the department of clinical surgery at Edinburgh University, delivered the Shepherd Lecture at the Montreal General Hospital on Monday, October 28. Shepherd's era, he emphasized, was almost the last in which a surgeon was able from his own resources to recognize and execute all that was known to be necessary for the care of a patient. Today, extended teamwork is essential; the radiologist, the biochemist, the clinical pathologist and the physician have each an important contribution to make to the successful outcome of modern surgical care. Intimate association of medical colleagues of equal standing pays a rich dividend. Following this line of thought, Professor Bruce urged that the same degree of higher integration should be carried over into medical education. We tend to build the student's edifice of knowledge in a series of slabs, with a difference in the emphasis with which each layer is at present applied. This leads only to confusion and should be eliminated by the teaching of large tracts of medicine and surgery as a single discipline.

Dr. J. W. McKay, chairman of the medical board of the hospital, presided. Professor Bruce was introduced by Dr. P. G. Rowe, surgeon-in-chief, and thanked by Dr. S. J. Martin, senior surgeon.

Before giving the Shepherd Lecture, Professor Bruce unveiled the foundation stone of the Jubilee Nurses' Home of the Montreal General Hospital. This was the first home erected by the hospital to serve as a residence for nurses. Its foundation stone was laid by Lord Lister on September 2, 1897. When the hospital moved to Cedar Avenue, the stone was removed from the original building on the Dorchester Street site and placed in front of Livingston Hall, the nurses' residence of the new hospital building. The name of the home commemorates Queen Victoria's Jubilee.

The scientific program for the session 1957-58 of the Montreal Medico-Chirurgical Society opened on November 1 with a symposium on the place of respiratory function tests in clinical medicine. Dr. Ronald V. Christie, physician-in-chief of the Royal Victoria Hospital and professor of medicine, McGill University, was the chairman. Members of the panel were Drs. L. Caswell, D. J. MacIntosh, D. V. Bates, P. Paré and Ronald Place. Dr. Christie first briefly reviewed the present-day tests of pulmonary function. Eight rather detailed case reports were then presented by the members of the panel; in every instance the significance of pulmonary function tests was reviewed in the light of the history and physical examination.

Dr. Newell W. Philpott, emeritus professor of obstetrics and gynaecology, McGill University, has

(Continued on page 1146)



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(Continued from page 1144)

been elected president-elect of the American College of Surgeons. This is the fourth time in the organization's 44-year history that a Canadian has been so honoured. Dr. Philpott will succeed to the presidency of the College at the meeting in Chicago next October.

Dr. Martin Y. Laberge, of Quebec, a graduate of the Laval University Faculty of Medicine in 1951, is the recipient of an award to recognize potential leadership, conferred by the Edward John Noble Foundation of New York City. Dr. Laberge has completed a fellowship in surgery at the Mayo Foundation Graduate School, University of Minnesota, at Rochester, Minnesota. A. H. NEUFELD

Dr. Bernard B. Raginsky, of Montreal, was elected president of the Academy of Psychosomatic Medicine at the fourth annual meeting, held October 17 to 19 in the Morrison Hotel, Chicago. Other officers are: Vice-president, Dr. Lester L. Coleman, New York City; Secretary, Dr. Wilfred Dorfman, Brooklyn, N.Y.; Treasurer, Dr. George F. Sutherland, Baltimore, Md.; Historian, Dr. Maury Sanger, Brooklyn, N.Y.; and President-elect, Dr. William S. Kroger, Chicago, Ill.

### ONTARIO

Dr. Gordon Copping, Montreal, addressed the Essex County Medical Society on November 6. His topic was recent advances in thyroid therapy.

The Ontario Hospital Association has elected the following officers: President, Harold M. Jackson, Simcoe; President-elect, Rev. James Ferguson, Barrie; Vice-presidents, Sister M. Emelda, London, J. E. Sharpe and M. B. Wallace, Toronto; Executive Secretary-Treasurer, S. W. Martin, Toronto.

Dr. Harvey Agnew, Professor of Hospital Administration, University of Toronto, made some predictions about the future effect of Ontario's hospital insurance plan on hospital functions when he addressed the 33rd annual meeting of the Ontario Hospital Association.

He predicted the establishment of entire units designed solely for diagnostic purposes; these units would be maintained for short-stay patients who do not require total bed care. They would be planned to provide for an up-patient lounge room, dining room and an open sun deck, if possible. Such a unit would be heavily staffed by technical personnel, but would require few nurses. There would be strong concentration of x-ray and laboratory services.

He believed that long-term patients would be accommodated in a separate wing or building designed with recreational facilities.

He foresaw heavier demands for four-bed and single rooms and less for semi-private two-bed rooms. He said that elimination of a time limit of a hospital stay will make it necessary to develop a clearcut policy or bed shortage will become more acute. The biggest problem in hospital planning is not merely to be up to date, but to be sure that what is built now will be functional for the next 60 or 75 years.

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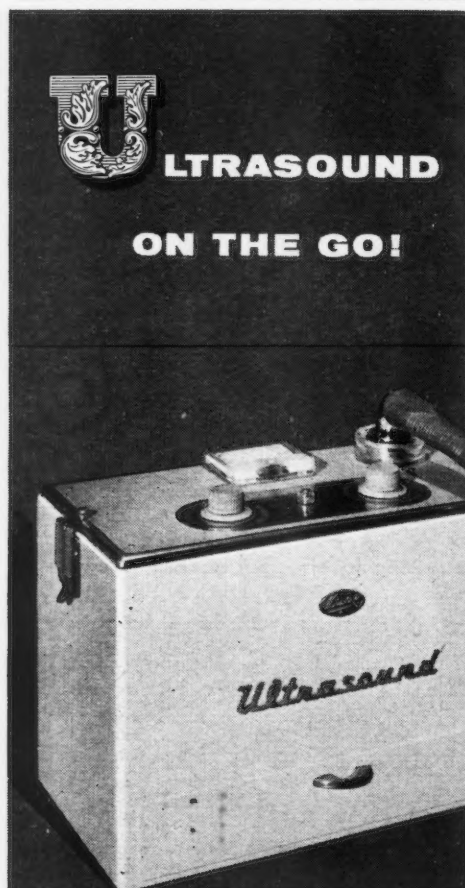
**MEDICAL NEWS in brief***(Continued from page 1124)***RE-APPOINTMENT OF  
WHO DIRECTOR-GENERAL**

Dr. M. G. Candau, Director-General of the World Health Organization, has accepted the offer made by the Tenth World Health Assembly last May to renew his contract for a second term.

Dr. Candau's present term of office expires on July 21, 1958, and he has asked for a renewal for two subsequent years. Dr. Candau, who was formerly in the public health service of Brazil, joined the staff of WHO in 1950 and held posts at headquarters in Geneva and also at the Pan American Sanitary Bureau, the regional office of the World Health Organization for the Americas.

**U.S. EDUCATIONAL  
COUNCIL FOR FOREIGN  
MEDICAL GRADUATES**

The U.S. Educational Council for Foreign Medical Graduates is now a going concern. The purpose of this organization is to carry out a detailed and comprehensive program for evaluating foreign medical-school graduates. It is an independent agency whose affairs are directed by a Board of Trustees designated by four co-operating organizations—the American Medical Association, the Association of American Medical Colleges, the American Hospital Association, and the Federation of State Medical Boards of the United States. For the next two years it will be supported by these four sponsoring agencies and by the Kellogg Foundation and the Rockefeller Foundation. The President of the Board is Dr. J. Murray Kinsman, Dean of the University of Louisville School of Medicine, and the Executive Director is Dr. Dean F. Smiley of Chicago, former Secretary of the Association of American Medical Colleges. For the asking, foreign medical graduates can obtain authentic information regarding the opportunities and difficulties involved in going to the United States on an exchange student visa in order to take training as an intern or resident in a U.S. hospital, or entering on an immigrant visa with the hope of becoming licensed to practise. The Council also will provide hospitals, State licensing boards and specialty boards with the results of the three-way screening of foreign medical graduates. It will also accumulate and publish each year complete data regarding the numbers and placement of foreign medical graduates in that country. Further information can be obtained from the Executive Director, Dr. Smiley, at the Orrington Hotel, Evanston, Illinois.

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FELLOWSHIPS**

For the purpose of stimulating medical research in Canada, l'Institut de Médecine et de Chirurgie expérimentales of the Université de Montréal will award three post-doctoral research fellowships to young Canadians of unusual promise and ability who wish

*(Continued on page 38)*





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#### MEDICAL NEWS in brief

(Continued from page 36)

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Each of these three fellowships will be in the amount of \$4000 for the first year (1958-1959), subject to an increase commensurate with results obtained and personal qualifications.

Applications, consisting of a letter accompanied by a curriculum vitae and an official transcript of Medical School record, should be addressed, on or before January 31, 1958, to: l'Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, P.O. Box 6128, Montreal, Quebec.

#### HABILITATION OF CHILDREN

Dr. Harold V. Cranfield, Consultant in Physical Medicine to the

Toronto Hospital for Sick Children, delivered an address on the rehabilitation of crippled children at the 9th annual medical alumni meeting. After defining the present scope of physiotherapy, he made a plea for the use of the term "habilitation" rather than "rehabilitation" in the case of handicapped children, since these children had in many instances known no better physical state. Early habilitation was essential for if they were left in their crippled state for a few years, the harm done to the personality was incalculable, and it would be necessary first to cure their mental disability. The crippled child presented a continuing chronic problem in each case; personality might well disintegrate unless care was taken to prevent overdependence on the part of the child and overprotection on the parents' part. The child required affection, education, a satisfactory body image and an opportunity to make his contribution to society. To acquire a satisfactory body image, the crippled child needed constant support and encouragement in his little victories.

#### U.S. BIOPHYSICAL SOCIETY

The Biophysical Society was organized and held its first national meeting at Columbus, Ohio, in March of this year. Although no formally organized Biophysical Society existed at that time, over 500 scientists attended the meeting and over 200 of them presented papers.

The first regular national meeting of the new society will be held at the Massachusetts Institute of Technology in Cambridge, Mass., on February 5, 6 and 7, 1958.

The Biophysical Society faces the unusual task of welding together into a new scientific team experts from such seemingly unrelated disciplines as physics, biology, medicine, chemistry, mathematics and engineering. From this union it is expected that there will arise a generation of scientific investigators, teachers, and applied scientists broad enough in their training and yet sufficiently expert in each constituent field to pursue effectively the new science of biophysics.

Biophysics, which is really only the application of the physical scientist's habits of thought and experimentation to problems of living things, is not really new but was a frequent occupation or avocation of most of the great physical scientists of a century or more ago before the scientific fad of narrow specialization became popular. This return towards a more complete biological science with emphasis upon creation of mathematically formalized theory and quantitative experimentation suggests an effective start towards a new and deeper insight into life processes as well as an opportunity for utilizing this insight in controlling environment and improving human well-being and satisfying basic curiosity about nature.

Because of the wide variety of scientists who will participate in the coming Biophysical Society meeting, a somewhat unusual plan of meetings has been adopted. On each of the three afternoons there will be a plenary session. Each year, one or two subjects will be made key themes of the entire meeting so as to make the meeting especially attractive to men in these fields. Two of the three plenary sessions will be on the special thematic topics while the third will be devoted to less extensive reviews

(Continued on page 40)

### MEDICAL OFFICERS

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## MEDICAL NEWS in brief

(Continued from page 38)

of three other currently important researches. Thus over a period of years all fields of biophysics can be covered.

The mornings will be devoted to a large number of parallel sessions of short contributed papers where specialists can deal more technically with their own problems. These sessions will not be limited to the special subjects but will be arranged to cover any biophysical topics in which papers are submitted.

Because it realizes that the subject matter of biophysics is not yet firmly fixed, the Society will accept papers from any qualified scientist who thinks he has biophysical material to present, whether he is a member of the society or not and whether he regards himself primarily as a biophysicist or not.

This year the special subjects to be intensively studied are in molecular biophysics. The first plenary session will be on *Microsomal Particles and Protein Synthesis* and the second on *Muscle Proteins and Contractile Mechanisms*.

The program chairman is Dr. A. K. Solomon, Biophysical Laboratory, Harvard Medical School, Boston, Mass.

## INFLUENZA IN CANADA

Health officers in the Province of Quebec have reported that the epidemic is nearly over. It started at the beginning of September, travelled from west to east, and is now on the wane in the Gaspé Peninsula. Complications of the illness reported from Alberta include epistaxis, pneumonia, otitis media and dermatitis. In British Columbia, school absenteeism is back to the normal rate for this time of the year. Reports from the Indian Health Services show that in July about half the population of LaRonge was affected by an epidemic due to an infection with influenza virus, type A variant. In September and October the same population suffered the impact of the Asian strain type of influenza and it is pointed out that the disease has been much more severe, with complications, in the Indian population. Four hundred and eighty-five cases were reported in the armed services in late November, with no further complications.

COMPARISON OF FAT  
INTAKE OF AMERICAN  
MEN AND WOMEN:  
POSSIBLE RELATIONSHIP  
TO INCIDENCE OF  
CLINICAL CORONARY  
ARTERY DISEASE

Recently a number of epidemiologic studies have been published concerning the possible causes of the relative immunity of various classes and groups of non-American men to overt coronary artery disease. Since a low-fat intake was thought to be a trait common to all of these groups, it was concluded that this dietary habit was chiefly responsible for the observed relative infrequency of clinical coronary artery disease in these persons. Impressive as is this relative immunity, immunity of the young premenopausal American woman of any class is perhaps even more striking. Thus, before the age of 40, if she is neither hypertensive nor diabetic, she exhibits more than 20 times more resistance to symptomatic coronary disease than does her American male counterpart.

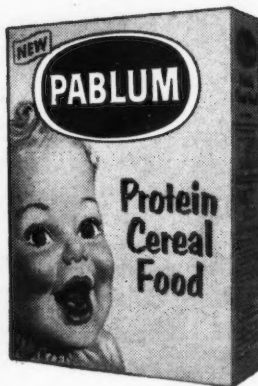
(Continued on page 42)



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### MEDICAL NEWS in brief

(Continued from page 40)

In order to study this problem, a detailed dietary history was obtained of 46 women and their husbands, members of an upper economic stratum. No significant difference was found in the caloric or percentage fat intake of each sex, when corrected for differences in surface area.

A critical review by Friedman and Roseman (*Circulation*, 16: 339, 1957) of various data relating to the relative immunity of the American woman to clinical coronary artery disease suggests that this immunity cannot be due entirely to some endocrine-induced protection against the supposed atherogenic properties of a high-fat dietary.

A similar review was made of the data relating the high intake of fat to the increased incidence of clinical coronary artery disease as observed in the American male. It was concluded that such a relationship is not only unproved but probably untenable. The possible atherogenic potential of the socio-economic stress peculiar to and characteristic of the middle- and upper-class male of Western society is discussed.

### CAUSES OF DEATH FROM TOTAL BODY IRRADIATION

Experimental radiation injury was studied in the laboratory by Allen and his colleagues to investigate the therapeutic aspects of a variety of agents. So far no treatment has been found that lowers the mortality rates at 300 r or more. Blood transfusions and broad-spectrum antibiotics are worth trying, but these measures combat secondary infection, anaemia or haemorrhage rather than the primary disorders of radiation. Ignorance of the cause of death from radiation alone is the problem. Blood and antibiotics are effective in minimally or non-irradiated casualties and should be saved for these in an atomic disaster.

Desquamation within the alimentary and digestive tracts after total body radiation is prevented by shielding of the head. So far this is not understood.

Shielding a small portion of the red marrow in the dog afforded the best chance of survival. Similarly the successful transplantation of bone marrow, possible only in

pure strains of mice or identical twins, is the best treatment for individuals receiving otherwise lethal dosage. Pre-treatment by agents that temporarily reduce oxygen consumption also increases the tolerance for radiation.

Experiments using dogs seem applicable to man, with some exceptions such as the delayed onset of purpura, leukopenia and thrombocytopenia in man.

Tolerance for anaesthesia and surgical operations on the abdomen, chest (and extremities) appears to be normal in the first three to four days after radiation injury but it is greatly diminished for the next four to six weeks. Non-essential surgery should be delayed at least three months.—*Ann. Surg.*, 146: 322, 1957.

### SCALENE LYMPHADENOPATHY

Bennett and Carr removed both the right and the left scalene fat pads at the time of 74 postmortem examinations. Absence of palpable lymph nodes above the clavicles was the only criterion used in selection of these cases. In four cases no lymph nodes were found in the fat pads. Nodes were found in both pads in 25 cases, on the right side only in 16 cases, and on the left side only in 29 cases. The number of nodes found in the fat pads varied from one to four. The nodes were fixed in formalin, and microscopic sections were stained with haematoxylin and eosin. These sections were studied as unknowns, and a diagnosis was made. The diagnoses were then correlated with the intrathoracic diseases found at autopsy.

The results confirm previous reports of the value of biopsy of impalpable scalene lymph nodes in the diagnosis of intrathoracic disease. Examination of the scalene lymph nodes revealed evidence of the intrathoracic disease in 12 of the 18 cases of such disease. In no case did examination of the scalene nodes suggest a diagnosis which was not confirmed by the rest of the postmortem study. The microscopic diagnosis included sarcoidosis, primary and metastatic intrathoracic neoplasms, and acute and chronic leukaemia. The findings also support the suggestion that if the examination on one side is negative, the procedure should be repeated on the opposite side.—*Am. Rev. Tuberc.*, 76: 503, 1957.



### USE OF PREDNISONE IN CONGESTIVE HEART FAILURE

In a study conducted by Gutner and his colleagues (*Am. J. M. Sc.*, 234: 281, 1957) 11 patients in congestive heart failure requiring maintenance digitalis therapy were given prednisone orally in doses of 20 and 40 mg. daily. The urinary excretions of sodium, potassium, and 17-ketosteroids were observed before and after corticoid administration. There were increased sodium and potassium excretion, decreased 17-ketosteroid output, essentially no change in weight and blood pressure, and an amelioration of the cardiac status. The possible mechanisms of action of prednisone in congestive heart failure are discussed. The authors conclude that prednisone may safely be administered to patients in congestive heart failure, but it would seem that care should still be exercised in the administration of potent steroids.

### ATHEROSCLEROSIS IN AFRICA

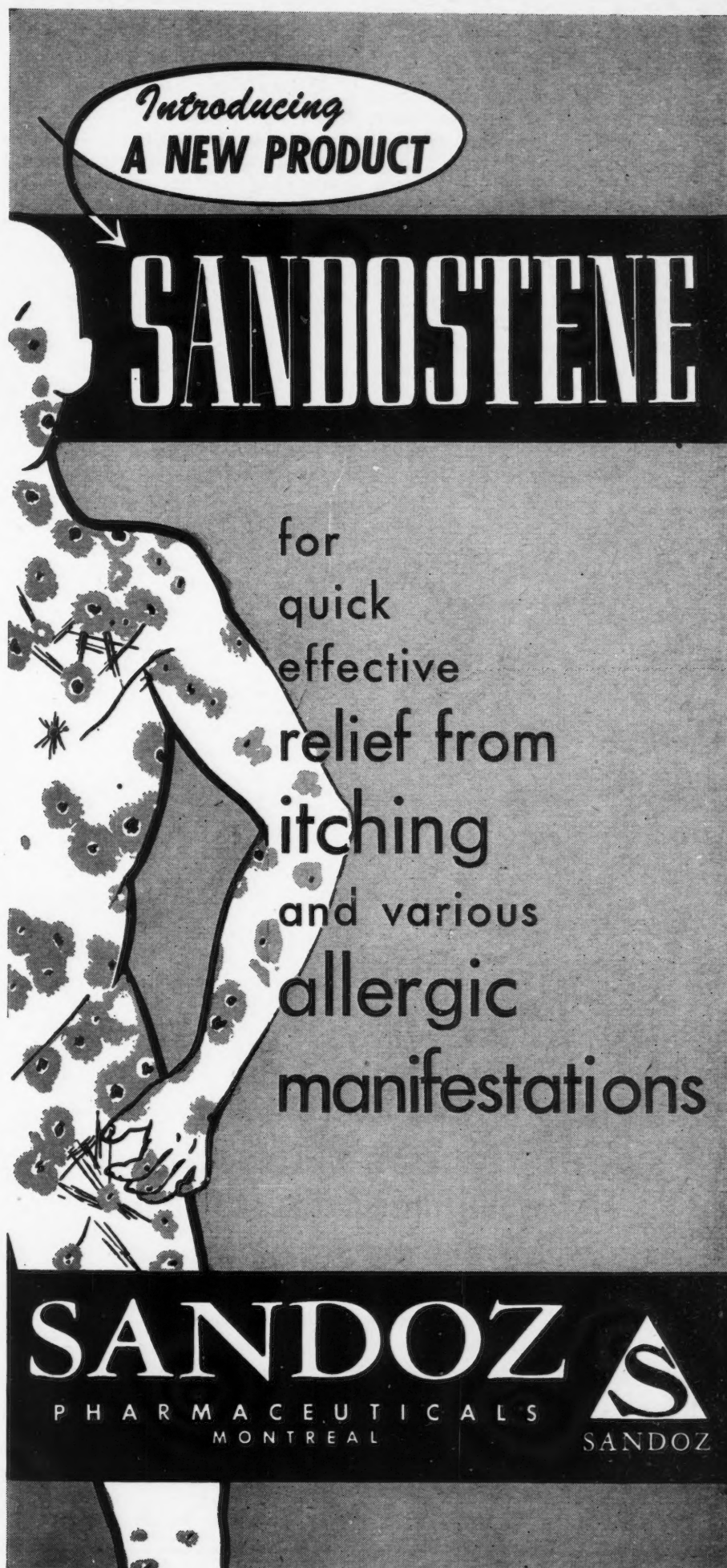
The incidence of atherosclerosis and heart disease varies in different parts of the world but is generally believed to be increasing everywhere. Smit (*South Africa J. Lab. & Clin. Med.*, 3: March 1, 1957) found a startling increase in the mortality rate from coronary artery disease when he investigated trends in cardiovascular disease among the white population of South Africa during the period 1926-54.

During this period the mortality rate from heart disease had doubled. Coronary disease has increased 16 times; the greatest increase for females has been in the 35-44 age group and for males in the 45-54 age group. Coronary disease now accounts for one-sixth of the total mortality and for 62.5% of all deaths from heart disease.

The increase described has affected both sexes, females slightly more than males. In 1954 heart disease accounted for 28.6% and 23.8% of total deaths of males and females respectively; coronary disease caused two of three male fatalities from heart disease and one of two female deaths.

In the younger age groups, relatively more males than females died

(Continued on page 44)




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SANDOZ

**MEDICAL NEWS in brief***(Continued from page 43)*

of coronary disease and there has been a relatively greater increase among males younger than 55 and females older than 55. The difference in mortality rate progressively decreased with the age of the group, and as the age of the group increases there appears to be a tendency for the rates for males and females to become equal. Mortality from general arteriosclerosis has decreased in all age groups except in those older than 75 years.

### ALLERGY TREATMENT IN RECURRENT NASAL POLYPOSIS: ITS IMPORTANCE AND VALUE

A group of 160 patients with mucous nasal polyps were observed over long periods of time while receiving allergy treatment. Of the entire group 72% had asthma, indicating that most polyp patients are potential asthmatics. This group could be subdivided into those that required not more than a single polypectomy (76 patients) and those that required multiple surgi-

cal procedures (84 patients). Since remissions were often spontaneous in the former, it was decided to judge the efficacy of allergy treatment in the latter group where the rate of recurrence was established.

Allergy treatment prevented recurrence in 46.8% of this latter group. An additional 21% were partially benefited, as judged by the lengthened interval between polypectomies. A group of 24 patients (31% of the recurrent group) failed to respond to allergy treatment, either alone or combined with other forms of therapy. In this group were many intractable asthmatics. Twenty patients (12.5%) of the entire series were aspirin-sensitive. Best results were obtained in the so-called "sensitive" group where specific allergies were identifiable and controllable.—G. I. Blumstein and L. Tuft: *Am. J. M. Sc.*, 234: 269, 1957.



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### TREATMENT OF TYPHOID FEVER

Two Italian authors have reported their results in the treatment with phenylbutazone of 24 patients suffering from typhoid or paratyphoid fever. The initial dose varied from 150 to 600 mg., depending on the age and weight of the patient. The medication was given as intramuscular injections or in the form of suppositories. The dosage was repeated q.12h. for three days and then slowly tapered off. All signs and symptoms subsided within a week of the onset of treatment. No untoward effect on the gastro-intestinal tract was noticed. All cases recovered except for one questionable relapse, which cleared up when treatment was resumed. The few side effects reported included a few bouts of furunculosis and one instance of bronchopneumonia. The results obtained are described as having been far superior to those secured by the most active antibiotic.

### PULSELESS OR TAKAYASU DISEASE

Pulseless disease is characterized by the absence of pulsations in the carotid and radial arteries. It may be caused by syphilitic arteritis or less frequently by syphilitic aneurysm. It occurs rarely in dis-

*(Continued on page 46)*



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## MEDICAL NEWS in brief

(Continued from page 44)

secting aneurysm and in traumatic injuries of the thorax. When these conditions have been excluded there remains a group of patients consisting predominantly of young and middle-aged women, in whom the etiology is unknown. A case which was observed over a period of years is presented by Kinney (*Am. Rev. Tuberc.*, 76: 79, 1957).

Symptoms in pulseless disease are predominantly those of occlu-

sion of the internal carotid artery; headache, vertigo, convulsion, paresis, and hemiplegia may occur. Hypersensitivity of the carotid sinus has complicated several cases. Ocular symptoms are often prominent, but in this case "intermittent claudication of vision" with exercise, and blurring and double vision on arising were the only symptoms. Cataracts, arteriovenous aneurysms, and slowing of the arterial circulation have been reported. In Japan the majority of these cases have been reported by

ophthalmologists. Symptoms from occlusion of the radial artery are conspicuous by their absence, since collateral circulation is adequate. Dyspnoea, chest pain and tachycardia have been reported. Systolic and diastolic murmurs have been noted in other reports.

Since the etiology is unknown, treatment is unsatisfactory. Long-term anticoagulant therapy has been used. With further advances in arterial surgery a surgical approach, although formidable, might be considered. The patient described here was treated symptomatically with papaverine during acute episodes and Priscoline for the long-term treatment. The patient died suddenly after three years; an occlusion of the right carotid artery just above its origin was found. The right subclavian artery showed partial occlusion of its lumen by an apparent subintimal thickening that began at its origin.

PULSELESS DISEASE DUE  
TO BRACHIAL ARTERITIS

Repeated reports from Japan and from north European countries have brought attention to a new clinical syndrome called "pulseless or Takayasu disease". The condition is found in young women and is characterized by thrombosis of the vessels deriving from the arch of the aorta associated with cerebral, ocular, and upper extremity symptoms. Its etiology is obscure.

Koszewski and Hubbard (*Circulation*, 16: 406, 1957) describe a case of pulseless disease or brachial arteritis and report findings of arteriography and arterial biopsy. The primary lesion seems to consist of an acute neutrophilic periarteritis progressing to panarteritis, causing arterial thrombosis. Later stages are characterized by fibroblastic hypertrophy of adventitia with lymphocytic and plasmacellular infiltrations.

The anatomic changes are characteristic enough for the condition to be regarded as an independent syndrome that can usually be well differentiated from other inflammatory and degenerative arterial diseases. The arteritis in this case seemed to respond to combined steroid and anticoagulant therapy.



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1. Smith, R. T.: *M. Clin. North America*, March 1957. 2. Smith, R. T.: *New York Med.* 5:16, 1952.  
3. Lehrer, H. W. et al.: *Northwest Med.* 75:1249, 1955.



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